PNS PERIPHERAL NERVE SOCIETY

2017 PNS Annual Meeting

8-12 July | Sitges, Spain

Programme and Abstracts

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2017
PNS Annual Meeting

8 – 12 July
Sitges, Spain

Welcome

On behalf of the Peripheral Nerve Society, we are delighted to welcome you to the 2017 Annual Meeting at the Meliá in Sitges, Spain.

The PNS Annual Meeting continues to be the premier meeting for cutting-edge innovation and advances in peripheral neuropathy. The 2017 Meeting will provide a mixture of excellent plenary lectures, oral platforms, oral posters, poster sessions, an education course and dedicated symposia organised by special interest groups for Charcot Marie Tooth and related neuropathies (CMTR), the Inflammatory Neuropathy Consortium (INC) and diabetes. There will also be clinical trials update sessions and a hot topic symposium. We look forward to you being part of it.

Join us for the Opening Ceremony on Saturday, 8 July, from 18.00 to 20.00, in the Auditorium Hall. The reception will feature complimentary drinks and hors d'oeuvres.

Coffee breaks and lunch for registrants will only be provided daily for registrants. Please see the programme for details.

Complimentary internet will be provided. Instructions for access can be found on page 11 of the programme. Be sure to attend the Business Meeting on Monday at 13.00 in the Main Auditorium. We will be reviewing Society business, and your input is needed.

Monday night, the PNS will be honoring Junior and new Members of the Society with a cocktail reception from 19.00 to 20.00.

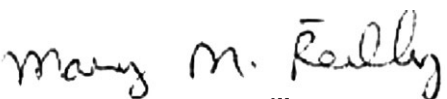
For those who have registered, please join us for the PNS Closing Dinner on Tuesday, 11 July, from 19.00 to 22.00 in the Tramuntana room. A pleasant and relaxing evening of camaraderie and networking is guaranteed. Prizes will be announced during the Closing Dinner.

Attendance to the Welcome Reception (Saturday 8 July from 18.00 to 20.00) and the Closing Dinner (Tuesday 11 July from 19.00 on) is only for those who signed up for these events during online registration.

The Junior and New Member Reception on Monday 10 July from 19.00 to 20.00 is open to everyone registered for the Meeting.

I want to personally thank the Scientific Programme Committee, Local Organising Committee, PNS Board, Meeting Faculty, and everyone else who has generously donated their time and efforts to put together this outstanding meeting.

I hope you enjoy the 2017 PNS Annual Meeting and your stay in Sitges.



Mary M. Reilly, MD
Peripheral Nerve Society
President

PERIPHERAL NERVE SOCIETY

Officers of the Society

Mary M. Reilly, President

Steven S. Scherer, President-Elect

David R. Cornblath, Secretary/Treasurer

Michael Polydefkis, Assistant Secretary/Treasurer

Board Members of the Peripheral Nerve Society

David Adams

Alessandra Bolino

Chiara Briani

Christopher Klein

Michael P.T. Lunn

Davide Pareyson

Inflammatory Neuropathy Consortium Representative

Richard Lewis

Charcot Marie Tooth and Related Neuropathies Consortium Representative

Davide Pareyson

Scientific Programme Committee

David Bennett, Co-chair

Lawrence Wrabetz, Co-chair

Scientific Review Committee

Jose Berciano

Wendy Campana

David R Cornblath

Susumu Kusunoki

Isabel Illa

Alison Lloyd

Xavier Navarro

Francesc Palau

Davide Pareyson

Michael Polydefkis

Luis Querol

Mary M. Reilly

Ricardo Rojas Garcia

Steven S. Scherer

Jordi Serra

Teresa Sevilla

Charlotte Sumner

Carla Taveggia

Pieter van Doorn

Local Organizing Committee

Isabel Illa, Chair

Jose Berciano

Xavier Navarro

Francesc Palau

Luis Querol

Ricardo Rojas Garcia

Jordi Serra

Teresa Sevilla

PNS Executive Office

Janel Fick - Executive Director

janelfick@PNSociety.com

Tanya Baker - Communications & Project Coordinator

info@PNSociety.com - www.pnsociety.com

Organizing Secretariat

the office

PNS2017@theoffice.it

www.theoffice.it/pns2017

The Society

The Peripheral Nerve Society was founded in 1994 from two groups of academic investigators, Peripheral Nerve Study Group and Peripheral Neuropathy Association of America, interested in the basic biology and function of the peripheral nervous system and its application to the clinic. Their invite only biennial meetings involved 80-125 attendees in cloistered settings organized by shoestring and local initiative. From this, we have grown remarkably. We now have an annual meeting of over 600 people including meetings within the meeting for the special interest groups in inflammatory, diabetic and hereditary neuropathy. With this substantial growth and the success of JPNS, the Journal of the Peripheral Nervous System, the Society continues to flourish.

2017 has proven to be a year full of exciting changes for the Society. PNS has transitioned from a biannual, to an annual meeting. Next year, the meeting will be taking place at the Renaissance Baltimore Harborplace Hotel from 22-25 July in Baltimore, Maryland. The development of a new website has been completed, please visit www.pnsociety.com to see the new face of the Society. Finally, PNS has adopted new Executive Staff. With their guidance and the leadership of an active and diverse Board of prominent professionals in the field the Peripheral Nerve Society continues to grow and anticipates more exciting changes in the year to come.

The Peripheral Nerve Society provides Annual Meetings, Teaching Courses, Guidelines, and other resources to aid in the education of members. Becoming a member of PNS means collaborating with prominent global professionals in the field to develop and provide the best treatments for people with peripheral nerve diseases and setting standards of care within the field. Please participate in our future by joining the PNS, volunteering for a project aligned with your interests and sending your ideas for the future to the Executive Office, or Board member.

PAST MEETINGS

Past Meetings of the PNAA and PNA

1984 Keystone, Colorado
1985 Keystone, Colorado
1986 Hilton Head Island, South Carolina
1988 Halifax, Nova Scotia, Canada
1989 Maui, Hawaii
1990 Oxford, England
1992 Rapallo, Italy

Past Meetings of the PNSG

1974 Carville, Louisiana
1975 Rochester, Minnesota
1977 Airlie House, Virginia
1979 Wye College, Kent, England
1981 Shakertown, Kentucky
1983 Fontevraud, France
1985 Mürren, Switzerland
1987 Lake Couchiching, Ontario, Canada
1989 Padua, Italy
1991 Arden House, New York
1993 Boppard, Germany

Past Meetings of the PNS

1994 Saint Paul, Minnesota
1995 Antalya, Turkey
1997 Cambridge, England
1999 La Jolla, California
2001 Tyrol, Austria
2003 Banff, Canada
2005 Tuscany, Italy
2007 Snowbird, Utah
2009 Würzburg, Germany
2011 Potomac, Maryland
2013 Saint-Malo, France
2015 Quebec City, Canada

Acknowledgments

Platinum sponsorship for the Meeting was provided by

Alnylam Pharmaceuticals, Inc.
CSL Behring
Grifols, S.A.
Kedrion S.p.A.
Pfizer, Inc. - Rare Disease
Terumo BCT, Inc.

Gold sponsorship for the Meeting was provided by

Shire, Plc

Silver sponsorship for the Meeting was provided by

GBS/CIDP Foundation International
Octapharma AG

Bronze sponsorship for the Meeting was provided by

Acceleron Pharma, Inc.
Ionis Pharmaceuticals, Inc.
LFB Biomedicaments
Mayo Medical Laboratories
Pharnext, SA

Sponsors

Hereditary Neuropathy Foundation
Syntimmune, Inc.
UCB Biosciences, Inc.

This support is gratefully acknowledged.

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92 Meeting participants
105 Abstracts

GENERAL INFO

ORGANIZING SECRETARIAT

The Meeting Secretariat will be open as follows:

Saturday 8 July 2017	8.00 – 19.00
Sunday 9 July 2017	7.00 – 19.00
Monday 10 July 2017	7.00 – 19.00
Tuesday 11 July 2017	7.00 – 19.00
Wednesday 12 July 2017	7.00 – 14.00

Starting from Friday July 7, you can reach the Secretariat at the following numbers

- Veronica Simeone **for participants** | mob **+39 338 3387766**
- Cristiana Fiandra **for sponsors** | mob. **+39 329 9449385**

REGISTRATION FEES

Registration Fees	Onsite fee
Member	€ 775,00
Junior / Trainee Member	€ 550,00
Non Member	€ 950,00
Junior / Trainee Non-Member	€ 550,00
Accompanying person	€ 370,00

Registration fees include attendance to the Scientific Sessions, the conference kit, coffee breaks, lunches, Welcome Reception (Saturday 8 July), Closing Dinner (Tuesday 11 July). Attendance to the Welcome Reception (Saturday 8 July from 18.00 to 20.00) and the Closing Dinner (Tuesday 11 July from 19.00 on) is only for those who signed up for these events during online registration. The Junior and New Member Reception on Monday 10 July from 19.00 to 20.00 is open to everyone registered for the Meeting.

ID BADGE

Your personal ID badge will be ready for you at the Meeting Registration Desk.
For security reasons, delegates, accompanying persons and exhibitors will be asked to wear their ID badges during the whole Meeting and at all social events.

CERTIFICATES OF ATTENDANCE

Your certificate should be requested via email (PNS2017@theoffice.it) after the Meeting.

WIFI

Make sure your wireless adapter is set to dynamically obtain an IP address
Connect to the wireless network: Melia

Enter credentials:
-Username: PNS2017
-Password: PNS2017

PRESENTATIONS

Oral presentation (platform)

The time allotted for Oral presentations **(O)** is 10 minutes + 5 minutes for questions for a total of 15 minutes. Only **PowerPoint presentations** are accepted.

Oral posters (OP)

Oral presentation during the oral poster session: time allotted is 3 minutes to briefly present the main message of your poster + 2 minutes for questions.

Put up Poster the evening before viewing.
Remove Poster at the end of the evening session.

Please note that all presentations should be uploaded in the room where you are going to talk.

Posters (P)

The number on each poster board corresponds to the number assigned in the abstract book.

Poster panel size: 37 inches wide x 43-59 inches high (95 cm wide x 110-150 cm high)

Put up Poster the evening before viewing.
Remove Poster at the end of the evening session.

EXHIBITION

An exhibition will take place during 2017 PNS Meeting.

OPENING HOURS	
Saturday 8 July 2017	14.00 – 18.00
Sunday 9 July 2017	8.30 – 18.00
Monday 10 July 2017	8.30 – 18.00
Tuesday 11 July 2017	8.30 – 18.00
Wednesday 12 July 2017	8.30 – 12.00

LIABILITY & INSURANCE

The Meeting Secretariat and Organizers accept no responsibility whatsoever for any injury or damage involving persons and property during the 2017 PNS Meeting.

Saturday 8 July 2017

MORNING

8.00	Registration Opening (AUDITORIUM HALL)
8.30 - 11.45	Individual Meetings 1: Inflammatory Neuropathy Consortium (TRAMUNTANA 1+2 ROOM)

AFTERNOON

12.00 - 14.00	PNS Board Meeting 1 (MESTRAL 1 ROOM) (Only Board Members are invited)
12.00 - 14.00	Lunch
14.00 - 18.00	Education Course (TRAMUNTANA 1+2 ROOM)

EVENING

18.00 - 20.00	Welcome Reception (AUDITORIUM HALL)
19.00 - 20.00	Put up posters for Poster Session 1 & Oral Poster Presentations Sessions 1 - 2 (TRAMUNTANA FOYER)

Sunday 9 July 2017

MORNING

7.30 - 8.30	Clinical Trial Updates (AUDITORIUM)
7.30 - 8.30	Poster Session 1 Viewing (TRAMUNTANA FOYER)
7.30 - 8.30	Coffee (TRAMUNTANA HALL)
8.30 - 9.00	Plenary 1: **RP Bunge Lecture** (AUDITORIUM) MOLECULAR ASPECTS OF THE FORMATION/MAINTENANCE OF THE NODE OF RANVIER **Elior Peles**
9.00 - 10.00	Platform Session 1 (AUDITORIUM)
10.00 - 10.30	Coffee (TRAMUNTANA HALL)
10.30 - 12.00	Oral Poster Presentations Session 1 (AUDITORIUM)

AFTERNOON

12.00 - 14.00	Poster Viewing (TRAMUNTANA FOYER)
12.00 - 14.00	Lunch
14.00 - 14.30	Plenary 2: **AK Asbury Lecture** (AUDITORIUM) CLINICAL ASPECTS AND NEW ANIMAL MODELS OF AUTO-IMMUNITY TO NODAL COMPONENTS **Isabel Illa**
14.30 - 15.30	Platform Session 2 (AUDITORIUM)
15.30 - 17.00	Oral Poster Presentations Session 2 (AUDITORIUM)

EVENING

17.00 - 18.00	Poster Viewing (TRAMUNTANA FOYER)
17.00 - 18.00	Coffee (TRAMUNTANA HALL)
18.00 - 19.00	Hot Topics Symposium (AUDITORIUM)
19.00 - 20.00	Alnylam Symposium (AUDITORIUM)
19.00 - 20.00	Grifols Symposium (TRAMUNTANA 1+2 ROOM)
19.00 - 20.00	Put up posters for Poster Session 2 & Oral Poster Presentations Session 3 (TRAMUNTANA FOYER)

Monday 10 July 2017

MORNING

7.30 - 8.30	Clinical Trial Updates **(AUDITORIUM)**
7.30 - 8.30	Poster Session 2 Viewing **(TRAMUNTANA FOYER)**
7.30 - 8.30	Coffee **(TRAMUNTANA HALL)**
8.30 - 9.00	Plenary 3: **JW Griffin Lecture** **(AUDITORIUM)** METABOLIC SUPPORT OF AXONS BY SCHWANN CELLS **Jeffrey Milbrandt**
9.00 - 10.00	Platform Session 3 **(AUDITORIUM)**
10.00 - 10.30	Coffee **(TRAMUNTANA HALL)**
10.30 - 12.00	Oral Poster Presentations Session 3 **(AUDITORIUM)**

AFTERNOON

12.00 - 13.00	Kedrion Symposium **(AUDITORIUM)**
12.00 - 13.00	Pfizer Symposium **(TRAMUNTANA 1+2 ROOM)**
13.00 - 13.30	PNS Business Meeting **(AUDITORIUM)**
13.00 - 14.30	Poster Viewing **(TRAMUNTANA FOYER)**
13.00 - 14.30	Lunch
14.30 - 19.00	Individual Meeting 2: Diabetes **(TRAMUNTANA 3 ROOM)**
14.30 - 18.30	Individual Meeting 2: Charcot-Marie-Tooth and Related Neuropathies (CMTR) **(AUDITORIUM)**
14.30 - 18.00	Individual Meeting 2: Inflammatory Neuropathy Consortium **(TRAMUNTANA 1+2 ROOM)**
19.00 - 20.00	Junior and New Members Reception **(TRAMUNTANA HALL)**
19.00 - 20.00	Put up Posters for Poster Session 3 & Oral Poster Presentations Sessions 4 - 5 **(TRAMUNTANA FOYER)**

Tuesday 11 July 2017

MORNING

7.30 - 8.30	Clinical Trial Updates (AUDITORIUM)
7.30 - 8.30	Poster Session 3 Viewing (TRAMUNTANA FOYER)
7.30 - 8.30	Coffee (TRAMUNTANA HALL)
8.30 - 9.00	Plenary 4: **PJ Dyck Lecture** (AUDITORIUM) MECHANOTRANSDUCTION AND PAIN **Gary Lewin**
9.00 - 10.00	Platform Session 4 (AUDITORIUM)
10.00 - 10.30	Coffee (TRAMUNTANA HALL)
10.30 - 12.00	Oral Poster Presentations Session 4 (AUDITORIUM)

AFTERNOON

12.00 - 13.00	CSL Behring Symposium (AUDITORIUM)
12.00 - 13.00	Terumo BCT Symposium (TRAMUNTANA 1+2 ROOM)
12.00 - 14.00	Poster Viewing (TRAMUNTANA FOYER)
12.00 - 14.00	Lunch
14.00 - 14.30	Plenary 5: **PK Thomas Lecture** (AUDITORIUM) THE CONTROL OF WALLERIAN DEGENERATION AND ITS RELEVANCE TO PERIPHERAL NEUROPATHY **Michael Coleman**
14.30 - 15.30	Platform Session 5 (AUDITORIUM)
15.30 - 17.00	Oral Poster Presentations Session 5 (AUDITORIUM)

EVENING

17.00 - 18.00	Poster Viewing (TRAMUNTANA FOYER)
17.00 - 18.00	Coffee (TRAMUNTANA HALL)
18.00 - 19.00	Presidential Talk - Prizes (AUDITORIUM)
19.00 - 22.00	PNS Closing Dinner (TRAMUNTANA ROOM)
19.00 - 20.00	Put up Posters for Poster Session 4 & Oral Poster Presentations Session 6 (TRAMUNTANA FOYER)

Wednesday 12 July 2017

MORNING

7.30 - 8.30	Clinical Trial Updates **(AUDITORIUM)**
7.30 - 8.30	Poster Session 4 Viewing **(TRAMUNTANA FOYER)**
7.30 - 8.30	Coffee **(TRAMUNTANA HALL)**
8.30 - 9.00	Plenary 6 **(AUDITORIUM)** NEURO-EPIDEMIOLOGY AND ITS RELEVANCE TO PHERIPHERAL NEUROPATHY **James J. Sejvar**
9.00 - 10.00	Platform Session 6 **(AUDITORIUM)**
10.00 - 10.30	Coffee **(TRAMUNTANA HALL)**
10.30 - 12.00	Oral Posters Presentation Session 6 **(AUDITORIUM)**

AFTERNOON

12.00 - 14.00	PNS Board Meeting 2 **(MESTRAL 1 ROOM)** (Only Board Members are invited)
12.00 - 14.00	Poster Viewing **(TRAMUNTANA FOYER)**
12.00 - 14.00	Lunch

Programme and Abstracts

SATURDAY 8 JULY 2017

8.00 Registration opening

8.30 - 11.45 **Individual Meeting 1: Inflammatory Neuropathy Consortium** TRAMUNTANA 1+2 ROOM
Chairs: **Richard Lewis** and **Ken Gorson**

8.30 - 9.15 Update on IGOS: **Bart Jacobs**
Update on CIDP Registries: **Filip Eftimov**
Update on IMAGiNe Project: **Mariëlle Pruppers**

9.15 - 9.45 Neuro-imaging studies in immune neuropathies
H. Stephan Goedee

Chair: **Susumu Kusunoki**
9.45 - 10.15 Complement dependence or independence in immune-mediated neuropathies
Hugh Willison, **Simon Rinaldi**

10.15 - 10.45 Break

10.45 - 11.15 Realistic goals in treating CIDP: Current and Future
Richard Lewis, **Ivo van Schaik**, **Eduardo Nobile-Orazio**

11.15 - 11.45 Discussion of the future of the INC and new projects proposals
Richard Hughes, **Richard Lewis**

12.00 - 14.00 **PNS Board Meeting 1** MESTRAL 1 ROOM
(Only Board Members are invited)

12.00 - 14.00 Lunch

14.00 - 18.00 **Education Course** TRAMUNTANA 1+2 ROOM
Chairs: **Alex Rossor** and **Chris Klein**

14.00 Clinical and electrophysiological phenotypes of inflammatory neuropathies
Yusuf Rajbally - Birmingham, United Kingdom

14.35 Muscle denervation and re-innervation in health and disease: A crash course
Charlotte Sumner - Baltimore, United States

15.10 Schwann cell biology in health and disease: A crash course
Alessandra Bolino - Milan, Italy

15.45 Break

Chairs: **Alex Rossor** and **Jean-Michel Vallat**

16.15 Next generation sequencing in Charcot-Marie-Tooth disease: (What it is (panels, WES, WGS), when to request, how to interpret, false positives and negatives)
Chris Klein - Rochester, United States

16.50 Crash course in the interpretation of peripheral nerve biopsies: which nerve to biopsy, tissue fixation: paraffin, semi thins, EM (common stains and immunos), identifying degenerating and regenerating axons, myelin, Schwann cells vs fibroblasts, onion bulbs
Jean-Michel Vallat - Limoges, France

17.25 Peripheral nerve biopsy – illustrative 'open' cases– delegates will be canvassed for cases to present prior to the meeting
Alex Rossor - London, UK

18.00 - 20.00 **Welcome Reception** **AUDITORIUM HALL**

19.00 - 20.00 Put up posters for Poster Session 1 &
Oral Poster Presentations Sessions 1 - 2 **TRAMUNTANA FOYER**

SUNDAY 9 JULY 2017

7.30 - 8.30 **Clinical Trial Updates** AUDITORIUM

Poster Session 1 Viewing TRAMUNTANA FOYER

(see end of Sunday 9 July 2017 for poster titles)

Coffee TRAMUNTANA HALL

Plenary Lecture and Platform Session 1 AUDITORIUM

Chairs: **Lawrence Wrabetz** and **Alexia Kagiava**

8.30 - 9.00 **Plenary 1: RP Bunge Lecture**

MOLECULAR ASPECTS OF THE FORMATION/MAINTENANCE OF THE NODE OF RANVIER

Elior Peles

9.00 - 10.00 **Platform Session 1**

9.00 **O1_1**

A NOVEL CMT2P MISSENSE MUTATION IN THE RING DOMAIN OF LRSAM1 IMPAIRS NUCLEAR TRANSLOCATION OF RNA-BINDING PROTEINS

Jun Li

(1) Hu B, (1) Arpag S, (2) Zuchner S, (1) Li J. (1) Department of Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA; (2) Hussman Institute for Human Genomics, University of Miami, Miami, Florida, USA

9.15 **O1_2**

A RAT MODEL OF CMT2A DEVELOPS A PROGRESSIVE NEUROPATHY

Steven Scherer

(1) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; (2) PsychoGenics, Tarrytown, NY, USA; (3) California Institute of Technology, Pasadena, CA, USA; (4) Renovo Neural Inc, Cleveland, OH, USA; (5) University of Wisconsin, Madison, WI, USA; (6) HumanFirst Therapeutics LLC, Silver Spring, MD, USA

9.30 **O1_3**

TRANSCRIPTIONAL AND TRANSLATIONAL PROFILING AND PRECLINICAL TESTING IN GARS/CMT2D MOUSE MODELS

Robert Burgess

(1, 2) Burgess RW, (1,2) Morelli KH, (1,2) Spaulding EL, (1) Seburn KL, and (3) Harper SQ. 1. The Jackson Laborary, Bar Harbor, ME USA; (2). The Graduate School of Biomedical Science and Engineering, University of Maine, Orono, ME USA 3 Center for Gene Therapy, The Research Institute at Nationwide Children's Hospital, Columbus, Ohio, USA

9.45 **O1_4**

RALGTPASES CONTROL SCHWANN CELL'S REPAIR FUNCTION AFTER NERVE INJURY BY CONTROLLING LAMELLIPODIA FORMATION

Jorge Galino

(1) Galino J, (1) Cervellini I, (1) Zhu N, (1) Stöberl N, (1) Fricker FR, (1) Lee G, (1) Hütte M, (2) Lalli G, (1) Bennett DL. (1) The Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, OX3 9DU UK; (2) Wolfson CARD, King's College London, Guy's Campus, London, SE1 1UL, UK.

10.00 - 10.30 Coffee TRAMUNTANA HALL

10.30 - 12.00 Oral Poster Presentations Session 1 AUDITORIUM

Chairs: **Alessandra Bolino** and **Dana Bis**

OP1_1 NODES OF RANVIER IN SKIN BIOPSIES OF PATIENTS WITH DIABETES MELLITUS

Claudia Sommer

(1) Doppler, K, (1) Frank, F, (3) Koschker, A-C, (1) Reiners, K, (1) Sommer, C. (1) Department of Neurology, University Hospital Würzburg Würzburg, Germany, (2) Endocrinology and Diabetes Unit, Department of Medicine I, University Hospital Würzburg, Würzburg, Germany

OP1_2 ALTERED POTASSIUM CHANNEL DISTRIBUTION AND COMPOSITION IN MYELINATED AXONS SUPPRESSES HYPEREXCITABILITY FOLLOWING INJURY

Margarita Calvo

(1) Calvo M, (2) Richards N, (3) Schimd A, (2) Barroso A, (2) Zhu L, (1) Ivulic D, (3) Zhu N, (1) Anwandter P, (4) Bhat M, (1) Court F, (2) McMahon SB, (3) Bennett DLH (1) Pontificia Universidad Catolica de Chile, Santiago, Chile; (2) Wolfson CARD, Kings College London, UK (3) NDCN Oxford University, UK (4) UT Health Science Center, San Antonio, TX, USA

OP1_3 N-METHYL-D-ASPARTATE RECEPTOR (NMDA-R) ACTIVATED CELL-SIGNALING IN RESPONSE TO GLUTAMATE IN SCHWANN CELLS

Wendy Campana

(1,3) Campana WM, (2,4) Mantuano E, (2) Azmoon P, (1) Henry KW, (1) Shibayama M, (1) Kim J, (2) Pizzo J, (2) Banki M, (2) Gonias SL. (1) Departments of Anesthesiology, UCSD School of Medicine, La Jolla CA, USA; (2) Departments of Pathology, UCSD School of Medicine, La Jolla CA, USA; (3) Program in Neurosciences, UCSD School of Medicine, La Jolla CA, USA; (4) Department of Experimental Medicine, Sapienza University of Rome, Rome, Italy

OP1_4 MILD ERK/MAPK ACTIVATION IN ADULT SCHWANN CELLS NEGATIVELY AFFECTS AXON SURVIVAL, MYELIN STABILITY AND SMALL FIBRES REINNERVATION AFTER NERVE INJURY

Ilaria Cervellini

(1) Cervellini I, (1) Galino J, (1) Zhu N, (2) Birchmeier C, (1) Bennett DL. (1) NDCN University of Oxford, Oxford, UK; (2) Max-Delbrück- Center for Molecular Medicine, Berlin, Germany

OP1_5 AUTOANTIBODIES TO NODAL ISOFORMS OF NEUROFASCIN IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Emilien Delmont

(1, 2)Delmont E, (2)Manso C, (3)Querol L, (4)Cortese A, (4)Berardinelli A, (2)Belghazi M, (5)Malissart P, (5)Labauge P, (5)Taieb G, (6)Yuki N, (3)Illa I, (1)Attarian S, (2)Devaux J. (1)Referral Center for ALS and Neuromuscular Diseases, La Timone University Hospital, Aix-Marseille University, France. (2)Aix-Marseille Université, CNRS, CRN2M-UMR7286, Marseille, France. (3) Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autónoma de Barcelona, Barcelona, Spain. (4)IRCCS, C. Mondino National Neurological Institute, Pavia, Italy. (5) Department of Neurology, Gui de Chauliac Hospital, Montpellier University Hospital Center, Montpellier, France. (6) Department of Neurology, Mishima Hospital, Niigata, Japan

OP1_6 ANTI-NFASC155 IGG4 AFFECT PARANODE STRUCTURE IN ANIMAL MODELS

Jerome Devaux

(1) Manso C, (2) Querol L, (1) Mekaouche M, (2) Illa I, (1) Devaux J. (1) Aix-Marseille Université, Marseille, France; (2) Universitat Autónoma de Barcelona, Barcelona, Spain

OP1_8 GENOME-WIDE ASSOCIATION STUDY IDENTIFIES POTENTIAL GENETIC MODIFIERS IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

Stephan Zuchner

(1) Tao F, (1) Beecham G, (1) Blanton S, (1) Abreu L, Inherited Neuropathy Consortium, (2) Baas F, (3) Choi BO, (4) Pareyson D, (5) Reilly M, (6) Shy M, (1) Zuchner S. (1) Dr. J.T. MacDonald Department for Human Genetics, Hussman Institute for Human Genomics, University of Miami, Miami, Florida, USA; (2) Department of Genome Analysis, Academic Medical Centre, Amsterdam, The Netherlands; (3) Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; (4) Department of Clinical Neurosciences, C. Besta Neurological Institute, Milan, Italy; (5) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK; (6) Department of Neurology, University of Iowa, Iowa City, Iowa, USA

OP1_9 LECITHIN LONG TERM THERAPY AMELIORATE DISEASE PROGRESSION IN A RAT MODEL OF CHARCOT MARIE TOOTH DISEASE 1A

Tamer Abdelaal
(1,2) Abdelaal T, (1) Fledrich R, (1) Rasch L, (1) Stenzel J, (1) Prukop T, (1,2) Stassart RM, (1) Nave KA, (1,3) Sereda MW. (1) Max-Planck- Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany; (2) University Medical Center Göttingen, Department of Clinical Neuropathology, Göttingen, Germany; (3) University Medical Center Göttingen, Department of Clinical Neurophysiology, Göttingen, Germany

OP1_10 FUNCTIONAL VALIDATION OF NON-CODING VARIANTS OF GJB1 IN PATIENTS WITH CMTX1

Andrea Cortese
(1) Cortese A, (2) Manole A, (3) Simone R, (2) Ashokkumar B, (1) Tomaselli PJ, (1) Rossor AM, (1) Laura M, (1) Gutowski J, (4) Polke H, (4) Poh R, (2) Houlden H, (1) Reilly MM. (1) MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, UK; (2) Department of Molecular Neuroscience, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, Queen Square, London, UK; (3) Department of Neurodegenerative Disease, UCL Institute of Neurology, Queen Square, London, UK; (4) Department of Neurogenetics, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK

OP1_11 DEVELOPMENT AND PILOT TESTING OF A FUNCTIONAL OUTCOME MEASURE FOR ADULTS WITH CHARCOT MARIE TOOTH NEUROPATHY (CMT-FOM)

David Herrmann
Eichinger KJ(1), Burns J (2), Cornett K(2), Bacon C(3), Shepherd M(4), Mountain J(1), Sowden J(1), Shy R(5), Shy ME(3), Herrmann DN (1)

OP1_12 A MULTICENTRE RETROSPECTIVE STUDY OF CHARCOT-MARIE-TOOTH DISEASE TYPE 4B (CMT4B)

Davide Pareyson
(1) Pareyson D, (2) Stojkovic T, (2) Leonard-Louis S, (3) Reilly MM, (3) Laurà M, (4) Parman Y, (4) Battaloglu E, (5) Tazir M, (5) Bellatache M, (6) Bonello-Palot N, (7) Sacconi S, (2) Guimarães-Costa R, (6) Attarian S, (8) Latour P, (2) Megarbane A, (9) Schenone A, (9) Ursino G, (10) Sabatelli M, (10) Luigetti M, (11) Santoro L, (11) Manganelli F, (12) Quattrone A, (12) Valentino P, (13) Murakami T, (14) Scherer SS, (14) Dankwa L, (15) Shy ME, (15) Bacon CJ, (16) Herrmann DN, (1) Pisciotta C, (1) Previtali S, (1) Bolino A. (1) Milan, (9) Genoa, (10) Rome, (11) Naples, (12) Catanzaro - Italy; (2) Paris, (6) Marseille, (7) Nice, (8) Lyon - France; (3) London - UK; (4) Istanbul - Turkey; (5) Algiers - Algeria; (13) Kurashiki - Japan; (14) Philadelphia, (15) Iowa City, (16) Rochester - USA

OP1_13 SCHWANN CELL-SPECIFIC DELETION OF THE ENDOSOMAL PI 3-KINASE VPS34 LEADS TO DELAYED RADIAL SORTING OF AXONS, ARRESTED MYELINATION, AND ABNORMAL ERBB2-ERBB3 TYROSINE KINASE SIGNALING

Fred Robinson
(1,2) Logan AM, (1,3) Mammel AE, (1,2) Robinson DC, (1) Chin AL, (1,2) Condon AF, (1,4) Robinson FL; (1) Jungers Center for Neurosciences Research, Department of Neurology, Oregon Health & Science University, Portland, Oregon, U.S.A.; (2) Neuroscience Graduate Program, Oregon Health & Science University, Portland, Oregon, U.S.A.; (3) Cell, Developmental & Cancer Biology Graduate Program, Oregon Health & Science University, Portland, Oregon, U.S.A.; (4) Vollum Institute, Oregon Health & Science University, Portland, Oregon, U.S.A

OP1_14 LIMITED SCHWANN CELL DIFFERENTIATION AS A PROTECTIVE MECHANISM IN CMT1B NEUROPATHY WITH ACTIVATED UNFOLDED PROTEIN RESPONSE

Francesca Florio
(1) Florio F, (1) Scapin C, (1) Ferri C, (2) Feltri M L, (2) Wrabetz L, (1) D'Antonio M. (1) (1) Myelin Biology Unit, San Raffaele Scientific Institute, Milan, Italy; (2) HJKRI-University of Buffalo, NY, USA

OP1_15 OPTIMIZING GENE EXPRESSION ANALYSIS IN CMT1A SKIN BIOPSIES

John Svaren
(1) Svaren J, (1) Moran JJ, (2) Wu X, (2) Gutmann L, (2) Shy M. (1) University of Wisconsin-Madison, Madison, WI; (2) University of Iowa, Iowa City, IA

12.00 - 14.00 **Poster Viewing** **TRAMUNTANA FOYER**

12.00 - 14.00 Lunch

Plenary Lecture and Platform Session 2 AUDITORIUM

Chairs: **Pieter van Doorn** and **Yoshikawa Keisuke**

14.00 - 14.30 Plenary 2: AK Asbury Lecture

CLINICAL ASPECTS AND NEW ANIMAL MODELS OF AUTO-IMMUNITY TO NODAL COMPONENTS

Isabel Illa

14.30 - 15.30 Platform Session 2

14.30 **O2_1**

TREATMENT RELATED FLUCTUATIONS AND ACUTE-ONSET CIDP IN THE IGOS COHORT

Carina Bunschoten

(1) Bunschoten C, (1) Miry F, (2) Vytopil M, (1) van Doorn PA, (1,3) Jacobs BC, the IGOS Consortium. (1) Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands; (2) Department of Neurology, Lahey Hospital & Medical Center, Burlington, USA; (3) Department of Immunology, Erasmus Medical Center, Rotterdam, The Netherlands

14.45 **O2_2**

PARANODAL DISSECTION IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY WITH ANTI- NEUROFASCIN 155 AND ANTI-CONTACTIN 1 ANTIBODIES

Haruki Koike

(1) Koike H, (2) Kadoya M, (2) Kaida K, (1) Ikeda S, (1) Kawagashira Y, (1) Iijima M, (3) Kato D, (4) Ogata H, (4) Yamasaki R, (3) Matsukawa N, (4) Kira JI, (1) Katsuno M, (1) Sobue G. (1) Nagoya University Graduate School of Medicine, Nagoya, Japan; (2) National Defense Medical College, Tokorozawa, Japan; (3) Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; (4) Kyushu University, Fukuoka, Japan

15.00 **O2_3**

ANTI-GM1 ANTIBODY MEDIATED MODELS OF AXONAL AND DEMYELINATING GBS IN GLYCOSYLTRANSFERASE- MODIFIED TRANSGENIC MICE

Rhona McGonigal

McGonigal R, Yao D, Barrie JA, Crawford C, Willison HJ. University of Glasgow, Glasgow, United Kingdom

15.15 **O2_4**

INVESTIGATION OF SERUM ANTIBODIES AGAINST GLYCOLIPIDS AND GLYCOLIPID COMPLEXES IN IMMUNE- MEDIATED NEUROPATHIES BY COMBINATORIAL GLYCOARRAY

Susumu Kusunoki

Kusunoki S, Morikawa M, Kuwahara M, Ueno R, Samukawa M, Hamada Y. Kindai University Faculty of Medicine, Osaka-Sayama, Japan

15.30 - 17.00 Oral Poster Presentations Session 2 AUDITORIUM

OP2_1 INTERLEUKIN 10 DEFICIENCY PARADOXICALLY PROTECTS FROM SPONTANEOUS AUTOIMMUNE PERIPHERAL NEUROPATHY IN A MOUSE MODEL OF CIDP

Collin-Jamal Smith

(1) Smith C, (2) Trout D, (3) Montgomery S, (4) Howard J, (5) Su M. (1) University of North Carolina at Chapel Hill, Chapel Hill, USA; (2) University of North Carolina at Chapel Hill, Chapel Hill, USA; (3) University of North Carolina at Chapel Hill, Chapel Hill, USA; (4) University of North Carolina at Chapel Hill, Chapel Hill, USA; (5) University of North Carolina at Chapel Hill, Chapel Hill, USA

OP2_2 Ca(2+)-DEPENDENT ANTI-GQ1B ANTIBODY IN FISHER SYNDROME: DETECTION AND INSIGHT INTO THE MOLECULAR MECHANISM

Atsuro Chiba

Chiba A, Uchibori A, Gyohda A. Kyorin University, Tokyo, Japan

OP2_3 JAPANESE ECULIZUMAB TRIAL FOR GUILLAIN- BARRÉ SYNDROME (JET-GBS)

Satoshi Kuwabara
(1) Kuwabara S, (1) Misawa S, (1) Sekiguchi Y, (2) Susumu Kusunoki, (3)JET-GBS Study Group. (1) Department of Neurology, Chiba University, Chiba, Japan; (2) Department of Neurology, Kindai University, Osaka, Japan; (3) Japanese Eculizumab trial for Guillain-Barré syndrome, Chiba, Japan

OP2_4 ANTIBODIES TO NEUROFASCIN155 IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: DIAGNOSTIC UTILITY OF A CONVENTIONAL ASSAY

Kenichi Kaida
(1) Kaida K, (1) Kadoya M, (2) Koike H, (2) Iijima M, (1) Takazaki H, (3) Ogata H, (1) Moriguchi K, (4) Shimizu J, (5) Nagata E, (5) Takizawa S, (6) Chiba A, (3) Yamasaki R, (3) Kira J-i, (2) Sobue G, (1) Ikewaki K. (1) National Defense Medical College, Tokorozawa, Japan; (2) Nagoya University Graduate School of Medicine, Nagoya, Japan; (3) Kyushu University, Fukuoka, Japan; (4) University of Tokyo, Tokyo, Japan; (5) Tokai University School of Medicine, Isehara, Japan; (6) Kyorin University, Tokyo, Japan

OP2_5 CLINICAL AND PATHOLOGICAL FEATURES IN FOUR PATIENTS WITH ANTI-NEUROFASCIN 155 IGG4 ANTIBODY-POSITIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Motoi Kuwahara
(1) Kuwahara M, (2) Oka N, (3) Ogata H, (1) Suzuki H, (1) Yanagimoto S, (1) Sadakane S, (1) Fukumoto Y, (1) Yamana M, (1) Yuhara Y, (1) Yoshikawa K, (1) Morikawa M, (1) Kawai S, (1) Okazaki M, (3) Kira J, (1) Kusunoki S. (1) Department of Neurology, Kindai University Faculty of Medicine, Osaka, Japan; (2) Department of Neurology, National Hospital Organization Minami-Kyoto Hospital, Kyoto, Japan; (3) Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

OP2_6 FREQUENCY AND ACTIVATION STATUS OF MYELOID CELLS IN THE GUILLAIN-BARRÉ SYNDROME

Ruth Huizinga
Wouter van Rijs, Willem Jan Fokkink, Anne Tio-Gillen, Maarten Brem, Bart Jacobs and Ruth Huizinga. Departments of Immunology and Neurology, Erasmus MC, University Medical Centre, Rotterdam, The Netherlands

OP2_7 ANTI-FGFR3 ANTIBODIES AND SENSORY-NEUROPATHY. A FRENCH PROSPECTIVE STUDY

Jean-Christophe Antoine
(1) Tholance Y, (1) Rosier C, (2) F Bouhour, (3) Psimaras D, (4) Kuntzer T, (5) Taieb G, (6) Créange A, (7) Delmont E, (1) Camdessanché JP,(1) Antoine JC. (1) University Hospital, Saint-Etienne, France; (2) University Hospital, Lyon, France; (3) University Hospital, Paris, France; (4) University Hospital, Lausanne, Switzerland; (5) University Hospital, Montpellier, France; (6) University Hospital, Creteil, France; (7) University Hospital, Marseille, France

OP2_8 EVALUATION OF DERMAL NERVE FIBERS IN CIDP NODO-PARANODOPATHY PATIENTS

Raffaella Lombardi
(1) Lombardi R, (2) Devaux J, (3) Cortese A, (1) Dacci P, (4) Benedetti L, (4) Demichelis C, (1) Lauria G. (1) IRCCS Foundation "Carlo Besta" Neurological Institute, Milan, Italy; (2) Aix-Marseille Université, Marseille, France; (3) IRCCS C. Mondino National Neurological Institute, Pavia, Italy; (4) University of Genova and IRCCS AOU San Martino-IST, Genova, Italy

OP2_9 IN VIVO IMAGING OF EPIDERMAL NERVE FIBERS

Gang Zhang
Zhang G, Ghosh P, Lin J, Ghauri A, and Sheikh KA. Department of Neurology, University of Texas Health Science Center at Houston, Houston, USA

OP2_10 INTERNATIONAL SECOND IMMUNOGLOBULIN DOSE IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME WITH POOR PROGNOSIS (I-SID GBS), A PROSPECTIVE OBSERVATIONAL STUDY

Christine Verboon
(1) Verboon C, (1) van den Berg B, (2) Cornblath DR, (1) Walgaard C, (3) Gorson KC, (4) Lunn MP, (5) Hartung HP, (6) Steyerberg EW, (6) Lingsma H, (1, 7) Jacobs BC, (1) van Doorn PA, the IGOS Consortium. (1) Department of Neurology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands (2) Department of Neurology, Johns Hopkins University, Baltimore, USA (3) Department of Neurology, Tufts University School of Medicine, Boston, USA (4) MRC Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery, London, UK (5) Department of Neurology, Heinrich Heine Universität, Düsseldorf, Germany (6) Department of Public Health, Erasmus Medical Centre, Rotterdam, The Netherlands (7) Department of Immunology, Erasmus Medical Centre, Rotterdam, The Netherlands

OP2_11 FUNCTIONAL AND MORPHOLOGICAL CONSEQUENCES OF CELLULAR AND HUMORAL RESPONSES IN TREATMENT-NAIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A COMBINED SONOGRAPHIC AND NERVE CONDUCTION STUDY

HS Goedee

(1,2) Goedee HS, (1,2) van der Pol WL, (1-3) Herraets IJT, (3) van Asseldonk JTH, (3) Visser LH, (1,2) van den Berg LH. (1) Department of Neurology, UMC Utrecht, Utrecht, The Netherlands (2) Brain Center Rudolf Magnus, Department of Neuroscience, UMC Utrecht, Utrecht, The Netherlands (3) Department of Neurology and Clinical Neurophysiology, St. Elisabeth Hospital, Tilburg, The Netherlands

OP2_12 RANDOMIZED CONTROLLED TRIAL OF ORAL FINGOLIMOD IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (FORCIDP TRIAL): PRIMARY AND SECONDARY OUTCOMES

Richard Hughes

(1) Hughes R, (2) Cornblath D, (3) Dalakas M, (4) Merkies ISJ, (5) Latov N, (6) Léger J-M, (7) Nobile-Orazio E, (8) Sobue G, (9) Genge A(10) Merschhemke M, (10) Ervin C, (10) Agoropoulou C, (11) Hartung H-P

OP2_13 EXPANDED B-CELL RECEPTOR CLONES ARE PRESENT IN PERIPHERAL BLOOD SAMPLES IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Gwen van Lieverloo

(1, 2) van Lieverloo G, (2) Musters A, (1) Adrichem M, (2) Esveldt R, (2) Doorenspleet M, (2) Klarenbeek P, (1) van Schaik I, (2) de Vries N, (1) F. Eftimov (1) Academic Medical Center, Department of Neurology, Amsterdam, the Netherlands (2) Academic Medical Center/University of Amsterdam, Department of Clinical Rheumatology and Immunology, Amsterdam, the Netherlands

OP2_14 REGULATORY B CELL FREQUENCIES INCREASE AFTER IVIG THERAPY IN INFLAMMATORY NEUROPATHIES

Ana Maria Siles

(1 2) Siles AM, (1 2) Assylbekova D, (1 2) Diaz-Manera J, (1 2) Rojas-Garcia R, (1 2) Cortes E, (1 2) Gallardo E, (1 2) Illa I, (1 2) Querol L. (1) Neuromuscular Diseases Unit, Neurology Department, Hospital de la Santa Creu i Sant Pau, Univeristat Autònoma de Barcelona, Barcelona (Spain); (2) Centro para la Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Madrid (Spain)

OP2_15 DEVELOPMENT OF A SUBACUTE ANTI-GANGLIOSIDE ANTIBODY-MEDIATED MOUSE MODEL OF GBS

Madeleine Cunningham

(1) Cunningham ME, (1) Yao D, (1) Meehan GR, (1) Barrie JA, (1) Willison HJ. (1) University of Glasgow, Glasgow, United Kingdom

17.00 - 18.00 **Poster Viewing** TRAMUNTANA FOYER

17.00 - 18.00 Coffee TRAMUNTANA HALL

18.00 - 19.00 **Hot Topics Symposium** AUDITORIUM

Chairs: **Charlotte Sumner** and **Alex Rossor**

18.00 **O3_1**

SUBCUTANEOUS IMMUNOGLOBULIN FOR MAINTENANCE TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP), A MULTICENTER RANDOMIZED DOUBLE-BLIND PLACEBO- CONTROLLED TRIAL: THE PATH STUDY

Ivo van Schaik

(1) van Schaik IN, (2) Bril V, (3) van Geloven N, (4) Hartung H-P, (5) Lewis RA, (6) Sobue G, (7) Lawo J-P, (7) Mielke O, (7) Durn BL, (8) Cornblath DR, (9) Merkies ISJ and on behalf of the PATH study group. (1) Department of Neurology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands; (2) Department of Medicine (Neurology), University Health Network, University of Toronto, Toronto, Canada; (3) Department of Biostatistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands; (4) Department of Neurology, Heinrich Heine University, Düsseldorf, Germany; (5) Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; (6) Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; (7) CSL Behring, Marburg, Germany and King of Prussia, PA, USA; (8) Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; (9) Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands

18.15 **O3_2**

THALIDOMIDE THERAPY FOR POEMS SYNDROME: A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL WITH LONG-TERM EXTENSION STUDY

Sonoko Misawa

(1) Misawa S, (2) Sato Y, (2) Katayama K, (1) Sekiguchi Y, (1) Amino H, (1) Suichi T, (1) Kuwabara S, and J-POST trial study group. (1) Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan; (2) Clinical Research Center, Chiba University Hospital, Chiba, Japan

18.30 **O3_3**

EFFECT OF PATISIRAN ON NERVE FIBER DENSITY AND AMYLOID CONTENT IN SKIN: RESULTS FROM PHASE 2 OPEN LABEL EXTENSION (OLE) STUDY IN hATTR AMYLOIDOSIS

Michael Polydefkis

(1) Polydefkis M, (1) Ebenezer G, (2) Adams D, (3) Coelho T, (4) Conceicao I, (5) Waddington Cruz M, (6) Schmidt H, (7) Buades J, (8) Campistol J, (9) Pouget J, (10) Berk J, (11) Partisano A, (11) Chen J, (11) Gollob J, (12) Suhr O. (1) Johns Hopkins University, Baltimore, USA; (2) National Reference Center for FAP (NNERF)/ APHP/ INSERM U 1195/ CHU Bicêtre, France; (3) Hospital de Santo António, Centro Hospitalar do Porto, Porto, Portugal; (4) Hospital de Santa Maria, Lisbon, Portugal; (5) Hospital Universitário, Federal University of Rio de Janeiro; Rio de Janeiro, Brazil; (6) University Hospital Münster, Munster, Germany; (7) Hospital Son Llatzer, Palma, Spain; (8) Hospital Clinic, University of Barcelona, Barcelona, Spain; (9) Hôpital de La Timone, Marseille, France; (10) Boston University, Boston, USA; (11) Alnylam Pharmaceuticals, Cambridge, USA; (12) Umeå University, Umeå, Sweden

18.45 **O3_4**

MRI QUANTIFICATION OF INTRAMUSCULAR FAT ACCUMULATION IN CMT1A: FOUR YEAR FOLLOW UP DATA

Jasper Morrow

(1) Evans ME, (1) Morrow JM, (2) Wastling S, (2) Sinclair CDJ, (3) Fischmann A, (2) Shah S, (2) Emira AK, (1) Hanna MG, (2) Yousry TA, (2) Thornton JS, (1) Reilly MM. (1) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK; (2) Neuroradiological Academic Unit, UCL Institute of Neurology, London, UK; (3) University of Basel Hospital, Basel, Switzerland

19.00 - 20.00 Sponsor Symposium 1: Alnylam AUDITORIUM

hATTR AMYLOIDOSIS - DIAGNOSTIC AND TREATMENT CHALLENGES: CAN WE IMPROVE THE CARE OF PATIENTS?

Objectives:

- To provide an overview of hereditary ATTR amyloidosis and the natural history of the disease
- To highlight the red flag symptoms and diagnostic pathway for hATTR amyloidosis
- To review the current treatment options and unmet needed of patients with hATTR amyloidosis
- To discuss emerging data from investigational medicines for patients with hATTR amyloidosis

Isabel Conceicao, Hospital Santa Maria, Lisboa - Portugal
Laura Obici, San Matteo Hospital, Pavia - Italy
Michael Polydefkis, Johns Hopkins Unversity, Baltimore - United States

19.00 - 20.00 Sponsor Symposium 1: Grifols TRAMUNTANA 1+2 ROOM

ANTIBODIES IN IMMUNE-MEDIATED NEUROPATHIES
Chair: **Isabel Illa**, Barcelona, Spain

19.00 SPIN Award Announcement & Introduction of Speakers
Isabel Illa, Barcelona, Spain

19.05 **Pathological Antibodies in immune-mediated Neuropathies.**
Overview of the importance of specific antibodies in the pathology of immune-mediated neuropathies
Luis Querol, Barcelona, Spain

19.20 **Autoimmunity to peripheral nerve proteins in acute and chronic neuropathies.**
Update onResearch into the presence of glycolipid Antibodies in CIDP and other autoimmune (inherited and acquired) Neuropathies
Eric Lancaster, Philadelphia, US

19.35 **The glyco-architecture of peripheral nerve: targets in autoimmune neuropathy.**
Overview of anti-glycolipid profiles in human autoimmune neuropathies, special focus on the importance of heteromeric glycolipid complexes
Hugh Willison, Glasgow, UK

19.50 Discussion
Isabel Illa, Barcelona, Spain

19.00 - 20.00 Put up posters for Poster Session 2 &
Oral Poster Presentations Session 3 **TRAMUNTANA FOYER**

Poster Session 1 TRAMUNTANA FOYER

P1_3 THE RELATIONSHIP BETWEEN MEDIAN SENSORY CONDUCTION OF MEDIAN NERVE AND ULNAR NERVE IN PATIENTS WITH CARPAL TUNNEL SYNDROME

Gulnihal Kutlu

(1) Unal Y, (1) Ozturk DA, (1) Emir GK, (2) Tosun K, (1) Kutlu G. (1) Mugla Sitki Kocman University Faculty of Medicine, Department of Neurology, Mugla, Turkey; (2) Mugla Sitki Kocman University Faculty of Medicine, Department of Biostatistics, Mugla, Turkey

P1_4 PAIN-RELATED SEP AFTER SELECTIVE A-DELTA- AND C-FIBER STIMULATION IN PATIENTS WITH NEUROPATHIC PAIN AND ITS POST-TREATMENT CHANGES

Sagiri Isose

(1,2) Isose S, (1) Watanabe K, (1) Omori S, (1) Sekiguchi Y, (1) Beppu M, (1) Shibuya K, (1) Amino H, (1) Suichi T, (1) Misawa S, (1) Kuwabara S

P1_5 USEFULNESS OF VARIOUS ULTRASONOGRAPHIC FINDINGS IN CARPAL TUNNEL SYNDROME

Hee Ju Kim

(1) Kim HJ, (2) Hyun JK, (3) Kim TU. (1) Dankook University, Cheonan, South Korea (2) Dankook University, Cheonan, South Korea (3) Dankook University, Cheonan, South Korea

P1_6 DOPPLER ULTRASONOGRAPHY FINDING BETWEEN PRE- AND POST- OPERATION IN CARPAL TUNNEL SYNDROME

Yasufumi Sekiguchi

Yasufumi Sekiguchi, Shin-ichi Kikuchi, Shin-ichi Konno and Miho Sekiguchi

P1_7 THE RELATIONSHIP BETWEEN CENTRAL AORTIC SYSTOLIC PRESSURE, PERIPHERAL BLOOD PRESSURE AND SYMPTOMATIC IN PATIENTS WITH AUTONOMIC DYSFUNCTION

Julia Ng

(1) Ng JPH, (2) Ng CJB, (3) T, Umapathi. (1) Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; (2) Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; (3) National Neuroscience Institute, Singapore, Singapore

P1_8 DEFINITION AND DIAGNOSIS OF SMALL FIBER NEUROPATHY (SFN): RECOMMENDATIONS FROM THE BRAZILIAN ACADEMY OF NEUROLOGY

Francisco Gondim

Gondim FAA; Barreira AA; Cruz MW; Cunha FMB; França Jr MC; De Freitas M; Marques Jr W; Nascimento OJM; Oliveira ASB; Pereira RC; Pupe C; Rotta FT; Schestatsky P. Panelists on behalf of the Scientific Department of Peripheral Neuropathy, Brazilian Academy of Neurology, Brazil

P1_10 ULTRASOUND FINDING IN ACUTE DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Jae Young An

(1) Bae DW, (2) An JY. (1) St. Vincent's hospital, The Catholic University of Korea, Suwon, Korea; (2) St. Vincent's hospital, The Catholic University of Korea, Suwon, Korea

P1_11 OCCURRENCE OF DIABETIC FOOT BY NCS-SEVERITY OF DIABETIC NEUROPATHY: A 5-YEAR PROSPECTIVE OBSERVATION

Masayuki Baba

(1) Baba M, (1) Suzuki C, (2) Ogawa C, (1) Tomiyama M. (1) Department of Neurology and (2) Diabetes Center, Aomori Prefectural Central Hospital, Aomori, Japan

P1_12 MITOCHONDRIAL OXODICARBOXYLATE CARRIER DEFICIENCY: METABOLIC MODELLING IDENTIFIES DISEASE MECHANISM

Veronika Boczonadi

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P1_13 RATS BRED FOR LOW AND HIGH RUNNING CAPACITY MAY OFFER A NEW MODEL OF INFLAMMATORY PAIN

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P1_14 CAPILLARY DYSFUNCTION IN THE DEVELOPMENT OF DIABETIC PERIPHERAL NEUROPATHY IN ANIMAL MODELS

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P1_15 MEDIAN NERVE ULTRASOUND MORPHOLOGY CADAVER SCREENING

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P1_16 CHARACTERIZING IN VITRO MODELS OF TYPE 2 DIABETIC PERIPHERAL NEUROPATHY

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P1_17 IN VITRO EFFECTS OF PURE GLYPHOSATE VS. GLYPHOSATE-BASED HERBICIDE ON PERIPHERAL NERVOUS SYSTEM MYELINATION

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P1_19 THE FORGOTTON CELL TYPE IN NEUROPATHIC PAIN: SATELLITE GLIAL CELLS

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P1_20 NEUROTOXICITY OF PACLITAXEL: IMPACT OF NANOPARTICLE - AND SOLVENT - BASED FORMULATION

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P1_21 ELECTRICAL STIMULATION AS A CONDITIONING LESION FOR PROMOTING PERIPHERAL NERVE REGENERATION

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P1_22 OBESITY ATTENUATES EPIDERMAL NERVE FIBERS IN THE DISTAL LIMB

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P1_23 IMAGING OF THE LOWER CRANIAL NERVES (LCN) IN THE EXTRACRANIAL COURSE

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P1_24 THE FUNCTIONAL IMPACT OF PERIPHERAL MYELIN PROTEIN 2 (PMP2) FOLLOWING DEMYELINATION IN VITRO AND VIVO

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P1_25 MARKED DECREMENT IN CMAP AMPLITUDE FOLLOWING PROLONGED EXERCISE IN SECONDARY HYPOKALEMIC PARALYSIS

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P1_26 THE FUNCTIONAL ROLE OF CONNEXINS IN PERIPHERAL MYELINATED FIBERS

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P1_27 FACIAL DIPLEGIA WITH BILATERAL FACIAL NERVE ENHANCEMENT AT 3T-MRI AND ANTI-GANGLIOSIDE ANTIBODIES

Marta Ruiz
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P1_28 NEWLY DEVELOPED WALDENSTROM MACROGLOBULINEMIA DURING IMMUNOMODULATORY TREATMENT FOR ANTI-MAG ANTI-SULFATIDE CIDP

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P1_29 LENALIDOMIDE-RESPONSIVE ANTI-MAG NEUROPATHY

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P1_30 NEUROPATHY AND PRIMARY HEADACHES DO NOT AFFECT THE SAME SUBGROUPS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

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P1_31 THE ROLE OF IMMUNOGLOBULIN G FC-GAMMA RECEPTOR POLYMORPHISMS IN THE PATHOGENESIS OF GUILLAIN-BARRÉ SYNDROME IN BANGLADESH

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P1_32 FUNCTIONAL FAS/FASL PROMOTER POLYMORPHISMS ASSOCIATED WITH INCREASED RISK OF NERVE DAMAGE IN GUILLAIN-BARRE´ SYNDROME IN BANGLADESH

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P1_33 RITUXIMAB IN INTRACTABLE CIDP

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P1_34 THE BURDEN AND JOURNEY OF PATIENTS WITH CIDP: A CASE-CONTROL ANALYSIS

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P1_36 NEUROPATHY AND PRIMARY HEADACHES DO NOT AFFECT THE SAME SUBGROUPS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

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P1_37 ACUTE DEMYELINATING POLYNEUROPATHY RESEMBLING GUILLAIN-BARRE SYNDROME IN A PATIENT TAKING THE SLIMMING PRODUCT PURA ALEGRÍA ®

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P1_38 ERAMUS GUILLAIN-BARRÉ SYNDROME RESPIRATORY INSUFFICIENCY SCORE IN JAPANESE PATIENTS

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P1_39 COEXISTENCE OF ACUTE DISSEMINATED ENCEPHALOMYELITIS AND GUILLAIN-BARRÉ SYNDROME WITH IG G ANTI-GT1A ANTIBODY POSITIVITY

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P1_40 A COMPARISON OF CLINICAL AND ELECTROPHYSIOLOGICAL PROFILES IN POEMS SYNDROME AND CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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P1_41 INVESTIGATION OF THE VARIATION OF MOTOR CONDUCTION VELOCITY BY USING HOPF`S COLLISION TECHNIQUE IN CIDP PATIENTS

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P1_42 TOTAL COMPOUND MUSCLE ACTION POTENTIAL DURATION: A NEW USEFUL ELECTROPHYSIOLOGICAL MEASURE FOR EARLY GBS DIAGNOSIS

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P1_43 CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY ASSOCIATED WITH LYMPHOMA : MONOCENTRIC STUDY

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P1_44 CONTRIBUTION OF PLEXUS MRI IN CIDP WITHOUT EFNS PNS DEFINITE ELECTROPHYSIOLOGICAL CRITERIA

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P1_45 SEMI-AUTOMATED MUSCLE MRI-VOLUMETRY FOR MYOPATHY AND NEUROPATHY PATIENTS

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P1_46 TREATMENT OF PARAPROTEINAEMIC NEUROPATHIES – A SINGLE-CENTRE AUDIT

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P1_47 GUILLAIN BARRÉ SYNDROME IN A HO CHI MINH CITY, VIETNAM HOSPITAL

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P1_48 SUBACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY WITH TREATMENT-RELATED FLUCTUATIONS

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P1_49 MARKERS AND INTENSIVE THERAPIES FOR GUILLAIN- BARRÉ SYNDROME WITH POOR PROGNOSIS; A RETROSPECTIVE STUDY IN JAPAN

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P1_50 CHANGES OF SERUM IGG DIMER LEVELS AFTER TREATMENT WITH IVIG IN GUILLAIN-BARRÉ-SYNDROME

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P1_51 COMPARISON OF TWO-YEAR RESPONSE TO LENALIDOMIDE OR PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION IN PATIENTS WITH POEMS

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P1_52 CLINICOPATHOLOGICAL FEATURES AMONG CIDP SUBTYPES

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P1_53 NEUROLOGICAL COMPLICATIONS IN MIDDLE EAST RESPIRATORY SYNDROME

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P1_54 NEUROPATHY IN RHEUMATOID ARTHRITIS: VASCULITIC OR IMMUNE-MEDIATED NEUROPATHY

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P1_55 PLEXIC MRI AND POSITRON EMISSION TOMOGRAPHY (PET) MERGE: A NEW TOOL FOR THE INVESTIGATION OF PERIPHERAL NERVES ?

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P1_56 NEUROFASCIN ANTIBODIES IN AUTOIMMUNE, GENETIC AND IDIOPATHIC NEUROPATHIES

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P1_57 AFTERDISCHARGES FOLLOWING M WAVES IN PATIENTS WITH VOLTAGE-GATED POTASSIUM CHANNELS ANTIBODIES

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P1_58 INFLUENCE OF BASELINE NEUROLOGIC SEVERITY ON DISEASE PROGRESSION AND THE ASSOCIATED DISEASE- MODIFYING EFFECTS OF TAFAMIDIS IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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P1_59 PRELIMINARY RESULTS FOR CHARCOT-MARIE-TOOTH PATIENT-REPORTED SURVEY

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P1_60 CHARCOT MARIE TOOTH DISEASE ASSOCIATED WITH AGENESIS OF THE CORPUS CALLOSUM: A HETEROGENEOUS ENTITY?

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P1_61 THE GENE MUTATION OF CHINESE PROBANDS WITH CHARCOT-MARIE-TOOTH DISEASE

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P1_62 DUPLICATION OF MYELIN PROTEIN ZERO CAUSING EARLY ONSET CHARCOT MARIE TOOTH DISEASE TYPE 1B

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P1_63 CLINICAL AND MAGNETIC RESONANCE IMAGING FEATURES OF THREE NOVEL MUTATIONS IN THE BICD2 GENE

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P1_64 GAIT IN CHILDREN AND ADOLESCENTS WITH CHARCOT-MARIE-TOOTH DISEASE: A CASE CONTROLLED STUDY OF GAIT IN DIFFERENT FOOTWEAR CONDITIONS

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P1_65 IMPAIRED MOTOR AXON EXCITABILITY IN A MOUSE MODEL OF CMT1A

Christian Krarup
(1) Alvarez S, (2) Klein D, (2) Martini R, (1,3) Moldovan M, (1,3) Krarup C (1) Center for Neuroscience, University of Copenhagen, Denmark; (2) Neurology, Developmental Neurobiology, University Hospital Würzburg, Germany; (3) Department of Clinical Neurophysiology, Rigshospitalet, Copenhagen, Denmark

P1_66 TARGETED NEXT-GENERATION SEQUENCING (NGS) PANELS IN CMT: A RETROSPECTIVE COMPARATIVE STUDY IN UK AND US TERTIARY REFERRAL CENTRES

Andrea Cortese
1) Cortese A, (2) Phetteplace J, (3) Polke J, (3) Poh R, (4) Houlden H, (1) Rossor AM, (1) Laura' M, (2) Shy ME, (1) Reilly MM. (1) MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, UK; (2) Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, US; (3) Department of Neurogenetics, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK; (4) Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK; National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

P1_67 IS PMP22 DUPLICATION THE ONLY COPY NUMBER VARIATION (CNV) RESPONSIBLE FOR CHARCOT-MARIE-TOOTH DISEASE? NEW CNV DISCOVERED USING COV'COP

Anne-Sophie Lia
(1) Miressi F, (1) Derouault P, (1,2) Dzugan H, (3) Cintas P, (1,2) Magdelaine C, (1,2) Sturtz F, (4) Merillou S, (1,2) Lia AS. (1) EA6309 – Université de Limoges, Limoges, France; (2) Service de Biochimie et Génétique Moléculaire - CHU de Limoges, Limoges, France; (3) Service de Neurologie et d'explorations fonctionnelles - CHU de Toulouse, Toulouse, France; (4) UMR7252-XLIM – Université de Limoges, Limoges, France

P1_68 CHARCOT-MARIE-TOOTH DISEASE TYPE 1C: CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS FOR THE C.334G>A (P.GLY112SER) LITAF/SIMPLE MUTATION

Nivedita Jerath
(1) Jerath NU, (1) Shy ME. (1) Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA

P1_69 EXTREME VARIABILITY IN DISEASE SEVERITY IN A FAMILY WITH A NOVEL EGR2 MUTATION

Shawna Feely
(1) Feely SME, (1) Saade D, (1) Shy ME. (1) University of Iowa Carver College of Medicine

P1_70 MUTATION SPECTRUM IN A TURKISH CHARCOT-MARIE-TOOTH DISEASE COHORT

Ayse Candayan
(1) Candayan A, (2) Atkinson D, (3) Durmus Tekce H, (3) Parman Y, (2) Jordanova A, (1) Battaloglu E. (1) Bogazici University Department of Molecular Biology and Genetics, Istanbul, Turkey; (2) Antwerp University, Center for Molecular Neurology, Antwerp, Belgium; (3) Istanbul University, Istanbul Medical School, Istanbul, Turkey

P1_71 SCREENING OF HINT1 MUTATIONS ASSOCIATED WITH RECESSIVE AXONAL NEUROPATHY IN A BRAZILIAN COHORT

Pedro José Tomaselli
(1) Rocha AM, (1) Tomaselli PJ, (2) Gouvea SP (2), (2) Figueiredo FB (2), (1) Lourenço CM (1), (1, 2) Marques W Jr. (1) Division of Neuromuscular Diseases, Department of Neurosciences and Behaviour Sciences, Clinical Hospital of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; (2) Neurogenetics, Department of Neurosciences and Behaviour Sciences, University of São Paulo, Ribeirão Preto, Brazil

P1_72 CHARCOT-MARIE-TOOTH DISEASE ASSOCIATED WITH DEAFNESS AND/OR SCOLIOSIS: NEW MUTATIONS DISCOVERED IN SH3TC2 GENE

Anne-Sophie Lia
(1) Lunati A, (1) Lerat J, (1,2) Dzugan H, (2) Rego M, (1,2) Magdelaine C, (4) Bieth E, (4) Calvas P, (5) Cintas P, (6) Gilbert-Dussardier B, (7) Goizet C, (8) Journel H, (9) Magy L, (10) Toutain A, (11) Urtizberea J, (1,2) Sturtz F, (1,2) Lia AS. (1) Service de Biochimie et Génétique Moléculaire - CHU de Limoges, Limoges, France; (2) EA6309 - Université de Limoges, Limoges, France; (3) Service Oto-rhino-laryngologie - CHU de Limoges, Limoges, France; (4) Service de Génétique Médicale - CHU de Toulouse, Toulouse, France; (5) Service de Neurologie et d'explorations fonctionnelles - CHU de Toulouse, Toulouse, France; (6) Service de Génétique Médicale - CHU de Poitiers, Poitiers, France; (7) Service de Neurogénétique - CHU de Bordeaux, Bordeaux, France; (8) Service de Génétique Médicale - Centre hospitalier Bretagne Atlantique, Vannes, France; (9) Service de Neurologie - CHU de Limoges, Limoges, France; (10) Service de Génétique Médicale - CHU de Tours, Tours, France; (11) Centre de référence Neuromusculaire - Hôpital marin, Hendaye, France

P1_73 AUTOSOMAL RECESSIVE MME MUTATIONS BROADEN THE CLINICAL PHENOTYPE ASSOCIATED WITH CMT2T

Vincenzo Lupo
(1,2) Lupo V, (3,4) Frasquet M, (1,2) Sánchez-Monteagudo A, (3) Barreiro M, (5) Alberti MA, (5) Casasnovas C, (4,6,7) Quintáns B, (8) Camacho A, (8) Domínguez C, (9) Sedano MJ, (9) Pelayo AL, (10) Pardo J, (10) Sobrino T, (4,6,7) Sobrido MJ, (3,4) Sevilla T, (1,2) Espinós C. (1) Centro de Investigación Príncipe Felipe, Valencia, Spain; (2) INCLIVA & IIS La Fe Rare Diseases Joint Units, Valencia, Spain; (3) Hospital Universitari i Politècnic La Fe, Valencia, Spain; (4) CIBER of Rare Diseases (CIBERER); (5) Hospital Bellvitge, Barcelona, Spain; 6Instituto de Investigaciones Sanitarias (IDIS), Santiago de Compostela, Spain; (7) Fundación Pública Galega de Medicina Xenómica, Santiago de Compostela, Spain; (8) Hospital 12 de Octubre, Madrid, Spain; (9) Hospital Universitario Marqués de Valdecilla, Santander, Spain; (10) Hospital Clínico Universitario Santiago de Compostela, Santiago de Compostela, Spain

P1_74 UPDATING THE CLASSIFICATION OF CMT AND RELATED NEUROPATHIES. RESULTS OF AN INTERNATIONAL SURVEY

Laurent Magy
(1) Magy L, (2) Mathis S, (3) Goizet S, (4) Tazir M, (1) Vallat J-M). (1) National reference center for rare peripheral neuropathies, Department and laboratory of Neurology, CHU Limoges, France; (2) Department of Neurology, CHU Bordeaux, France; (3) Department of Medical Genetics, CHU Bordeaux, France; (4) Department of Neurology, CHU Algiers, Algeria

P1_75 FUNCTIONAL OUTCOMES OF SURGICAL INTERVETIONS IN ADOLESCENTS WITH CHARCOT-MARIE-TOOTH DISEASE: A DETAILED EVALUATION USING MOTION ANALYSIS

Sylvia Ounpuu
(1,2) Õunpuu S, (1) Pogemiller K, (3) Acsadi G, and (1, 2, 4) Pierz K. (1) Center for Motion Analysis, Connecticut Children's Medical Center, Farmington, CT, USA, (2) School of Medicine, University of Connecticut, Farmington, CT, USA, (3) Division of Neurology, Connecticut Children's Medical Center, Farmington, CT, USA, (4) Division of Orthopaedics, Connecticut Children's Medical Center, Farmington, CT, USA

P1_76 DIAGNOSTIC CHALLENGES IN AMYLOID NEUROPATHIES

Michael Polydefkis
Polydefkis M, Neuhaus S, Doherty L, Ebenezer GJ. Department of Neurology, Johns Hopkins University, Baltimore, MD, USA

P1_77 TESTING OVERWORK WEAKNESS IN CHARCOT-MARIE-TOOTH (CMT) DISEASE: IS IT TRUE OR FALSE?

Valeria Prada
Prada V, Mori L, Francini L, Accogli S, Ursino G, Gemelli C, Schizzi S, Rivarola M, Grandis M, Bellone E, Mandich P, Schenone A. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health, University of Genoa, Genoa, Italy

P1_78 FUNCTIONAL CONSEQUENCES OF HIP DYSPLASIA IN PAEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

Leanne Purcell
(1,2) Purcell L, (1,2) Wojciechowski E, (1,2) Gibbons P, (1,3) Jamil K, (1,2) Menezes, M, (1,2) Burns J. (1) Sydney Children's Hospitals Network (Randwick and Westmead), New South Wales, Australia (2) University of Sydney, New South Wales, Australia (3) Universiti Kebangsaan, Kuala Lumpur, Malaysia

P1_80 CMT2B2 IN CZECH PATIENTS WITH DIFFERENT GLAUCOMA PHENOTYPES AND THREE NOVEL SBF2 MUTATIONS, ONE OF THEM DE-NOVO

Pavel Seeman
(1) Seeman P, (1) Laššuthová P, (1) Neupauerová J, (2) Mazanec R, (3) Senderek J (1) Dept of Pediatric Neurology, 2nd Medical Faculty, Charles University, Prague, Czech Republic; (2) Dept of Neurology, 2nd Medical Faculty, Charles University, Prague, Czech Republic (3) Friedrich Baur Institute, Ludwig – Maximilian University, Munich, Germany

P1_81 QUANTITATIVE MUSCLE ULTRASOUND AS A BIOMARKER IN CHARCOT-MARIE-TOOTH NEUROPATHY

Nortina Shahrizaila
(1,2) Shahrizaila N, (1) Noto Y, (3) Simon NG, (1) Huynh W, (1) Shibuya K, (1) Matamala JM, (1) Dharmadasa T, (1) Devenney E, (4) Kennerson ML, (4) Nicholson GA, (1) Kiernan MC (1) Brain and Mind Centre, University of Sydney, Camperdown, Australia (2) Department of Neurology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia (3) St Vincent's Clinical School, University of New South Wales, Darlinghurst, Australia (4) ANZAC Research Institute and Sydney Medical School, University of Sydney, Sydney, Australia

P1_82 CHARACTERISTIC OF RECOVERY FROM MUSCLE FATIGUE IN CHARCOT-MARIE-TOOTH PATIENTS WITH ELECTROMYOGRAPHIC STUDY (THIRD REPORT)

Toshinori Shimoi
(1) Shimoi T, (2) Yamada T (1) International University of Health and Welfare, Tochigi, Japan, (2) CMT Japan, Tokyo, Japan

P1_84 CHARCOT-MARIE-TOOTH DISEASE TYPE-2 ASSOCIATED WITH TWO MISSENSE MUTATION IN MME GENE

Elisa Vegezzi
(1) Vegezzi E, (2) Cortese A, (1) Callegari I, (2) Rossor AM, (3) Houlden H, (2) Reilly MM. (1) Neuroscience Consortium, University of Pavia, Monza Policlinico and Pavia Mondino, Italy; (2) MRC Centre for Neuromuscular

Diseases, National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, UK; (3) Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK; National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

P1_85 3D PRINTING ANKLE-FOOT ORTHOSES FOR CHILDREN WITH CMT: A REVIEW OF THE LITERATURE

Elizabeth Wojciechowski
(1,2) Wojciechowski E, (1) Chang A, (1,2) Cheng T, (1,2) Little D, (1,2) Menezes MP, (2) Hogan S, (1,2) Burns J. (1) University of Sydney, New South Wales, Australia; (2) Sydney Children's Hospitals Network (Randwick and Westmead), New South Wales, Australia

P1_86 THE EFFECTS OF A PHYSICAL THERAPY PROGRAM ON BALANCE, MOBILITY, AND QUALITY OF LIFE IN PATIENTS WITH CHARCOT-MARIE-TOOTH PERIPHERAL NEUROPATHY: A RETROSPECITVE REPORT

James Nussbaum
(1) James Nussbaum. (1) ProHealth & Fitness New York, NY

P1_87 A SENSITIVE MEASURE OF VIBRATION SENSE IN THE CMTNSv2

Chelsea Bacon
Bacon C, Feely SME, Shy ME. University of Iowa Hospital, Iowa City, IA, USA

P1_88 MRI FAT FRACTION OF TIBIALIS ANTERIOR MUSCLE CORRELATES WITH DISABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

Joachim Bas
(1) Bas J, (1, 2) Delmont E, (3) Le Troter A, (1) Fatehi F, (1, 5) Salort-Campana E, (1) Sévy A, (1) Verschueren A, (1, 5) Pouget J, (4) Lefebvre MN, (1) Grapperon AM, (3) Bendahan D, (1, 5) Attarian S. (1) Reference Center for Neuromuscular Diseases and ALS, La Timone University, Aix-Marseille University, Marseille, France; (2) Aix-Marseille University, UMR 7286, Medicine Faculty, Marseille, France; (3) CRMBM, CNRS, La Timone University Hospital, Aix-Marseille University, Marseille, France; (4) CIC-CPCET, La Timone University Hospital, Aix-Marseille University, Marseille, France; (5) Aix-Marseille University, Inserm, GMGF, Marseille, France

P1_90 CARDIAC SCINTIGRAPHY IS A USEFUL TOOL FOR THE DIAGNOSIS, PROGNOSIS AND PRE-SYMPTOMATIC EARLY DETECTION OF FAMILIAL AMYLOIDOSIS ASSOCIATED NEUROPATHIES

Tayla Romão
(1) Cavaliere MG, (2) Ferrari, AT, (3) Medeiros KQM, (4) Ferreira JMC, (5) Macedo PHA, (6) Westin LK, (7)Marques Jr W, (8) Romão T, (9) Bittar C, (10) Pupe C, (11) Nascimento OJM. Federal Fluminense institution, Rio de Janeiro, Brazi

MONDAY 10 JULY 2017

7.30 - 8.30 **Clinical Trials Update** AUDITORIUM

Poster Session 2 Viewing TRAMUNTANA FOYER

(see end of Monday 10 July 2017 for poster titles)

Coffee TRAMUNTANA HALL

Plenary Lecture and Platform Session 3

Chairs: **Carla Taveggia** and **Mansour Haidar**

8.30 - 9.00 **Plenary 3: JW Griffin Lecture** AUDITORIUM

METABOLIC SUPPORT OF AXONS BY SCHWANN CELLS

Jeffrey Milbrandt

9.00 - 10.00 **Platform Session 3** AUDITORIUM

9.00 **O4_1**

CONSERVED BIOENERGETIC SIGNATURE IN PERIPHERAL NERVE OF BKS-DB/DB AND HIGH FAT DIET MICE WITH NEUROPATHY

Lucy Hinder

Hinder LM, Backus C, Hayes JM, Feldman EL. University of Michigan, Ann Arbor, MI, USA

9.15 **O4_2**

MUTATION IN GLYCYL-tRNA SYNTHETASE IMPAIR MITOCHONDRIAL METABOLISM IN NEURONS

Veronika Boczonadi

(1) Boczonadi V, (2) Meyer K, (3,4) Gonczarowska-Jorge H, (1) Bartsakoulia M, (1,3) Roos A, (1) Bansagi B, (3) Zahedi RP, (5) Talim B, (6) Bruni F, (2,7) Kaspar B,(1) Lochmüller H, (8) Boycott KM, (1) Müller JS, (1) Horvath R. (1) JWMDRC, WTCMR, IGM, Newcastle University, Newcastle upon Tyne, UK, (2) RINCH, Columbus, Ohio USA; (3) Leibniz-Institute für Analytische Wissenschaften -ISAS- e.V., Dortmund, Germany;(4)CAPES Foundation, Brazil; (5) Department of Pediatrics, Hacettepe University Children's Hospital, Ankara, Turkey; (6) DBBB, University of Bari Aldo Moro, Bari, Italy; (7) Department of Neuroscience, The Ohio State University, Columbus; (8) Department of Genetics, CHEO, University of Ottawa, Ottawa, Canada

9.30 **O4_3**

CRITICAL ROLE FOR MONOCARBOXYLATE TRANSPORTER (MCT1) IN DEVELOPING AND REGENERATING PERIPHERAL NERVES

Brett Morrison

Jha MK, Russell K, Lee Y, Rothstein JD, Morrison BM. Departments of Neurology and Brain Science Institute, Johns Hopkins University School of Medicine, Baltimore MD, USA

9.45 **O4_4**

MUSCARINIC RECEPTOR SIGNALING CONSTRAINS AXONAL OUTGROWTH BY AUGMENTING DISSOLUTION OF THE CYTOSKELETON IN ADULT SENSORY NEURONS

Mohammad Golam Sabbir

Sabbir MG1, Calcutt NA2 and Fernyhough P1, 3. 1Division of Neurodegenerative Disorders, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada, 2Department of Pathology, University of California San Diego, California USA and 3Dept of Pharmacology & Therapeutics, University of Manitoba, MB, Canada

10.00 - 10.30 Coffee TRAMUNTANA HALL

10.30 - 12.00 Oral Poster Presentations Session 3 AUDITORIUM

Chairs: **Davide Pareyson** and **Paola Alberti**

OP3_1 DISTAL SENSORIMOTOR POLYNEUROPATHY FOLLOWING 13 YEARS OF TYPE 2 DIABETES ASSESSED BY THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT QUESTIONNAIRE. A PROSPECTIVE STUDY, THE ADDITION DENMARK STUDY

Troels Staehelin Jensen
(1,2) Andersen S T, (1,3) Witte D R, (1) Dalsgaard EM,(2,4) Andersen H, (5) Nawroth P, (5) Flemming T, (6) Jensen T M, (2,7) Finnerup N B, (2,7) Jensen T S, (1) Lauritzen T, (1,2) Charles M. (1)Department of Public Health, Aarhus University, Aarhus, Denmark; (2)International Diabetic Neuropathy Consortium, Aarhus, Denmark; (3) Danish Diabetes Academy, Odense, Denmark; (4) Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; (5)Department of Medicine I and Clinical Chemistry, University Hospital Heidelberg, Heidelberg, Germany; (6) Steno Diabetes Center, Copenhagen, Denmark; (7) Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

OP3_2 TREATMENT INDUCED NEUROPATHY OF DIABETES MELLITUS IS UNCOMMON IN A GENERAL DIABETES MELLITUS COHORT

Jasmine Koh
(1) Koh S, (2) Wong SHJ, (2) Loh KW, (3) Chng YSK, (3) Pawa C, (4) Ei MA, (2) Lee BJH, (5) Subramaniam T, (1) T. Umapathi. (1) National Neuroscience Institute, Singapore; (2) Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; (3) Yong Loo Lin School of Medicine, National University Singapore, Singapore; (4) Tan Tock Seng Hospital, Singapore;(5) Khoo Teck Puat Hospital, Singapore

OP3_3 DIFFERENTIAL EFFECT OF SATURATED AND UNSATURATED FATTY ACIDS ON MITOCHONDRIAL TRAFFICKING IN DORSAL ROOT GANGLION SENSORY NEURONS

Amy Rumora
(1) Rumora AE, (1) Hayes JM, (1) LoGrasso G, (1) Haidar J, (1) Dolkowski J, (2) Lentz SI, and (1) Feldman EL. (1) Department of Neurology, University of Michigan, Ann Arbor, MI 48109 USA; (2) Department of Internal Medicine, Division on Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, USA

OP3_4 RESPONSIVENESS OF CORNEAL CONFOCAL MICROSCOPY TO DIABETIC NEUROPATHY PROGRESSION

A. Gordon Smith
Smith AG, Thurgood B, Revere C, Hauer P, Aperghis A, Singleton JR University of Utah, Salt Lake City, Utah, USA

OP3_5 GENOMIC ANALYSIS REVEALS FREQUENT TRAF7 MUTATIONS IN INTRANEURAL PERINEURIOMAS

Michelle Mauermann
Klein CJ, Wu Y, Jentoft ME, Mer G, Spinner RJ, Dyck PJB, Dyck PJ, Mauermann ML. Mayo Clinic, Rochester, USA

OP3_6 IMPAIRMENT OF AUTOPHAGY AS A POSSIBLE PATHOMECHANISM FOR CMT CAUSING MUTATIONS IN HSPB1

Mansour Haidar
Haidar M, De Winter V, Asselbergh B, Bouhy D, Timmerman V. Peripheral Neuropathy Research Group, VIB, University of Antwerp, Antwerp, Belgium

OP3_7 CHARCOT-MARIE-TOOTH DISEASE TYPE 2G REDEFINED BY A NOVEL MUTATION IN LRSAM1

Paulius Palaima
(1) Palaima P., (1) Peeters K., (2) L. Pelayo-Negro A., (2) García A., (2) Gallardo E., (2) García-Barredo R., (1) De Vriendt E., (2) Infante J., (2) Berciano J., (1) Jordanova A. (1) VIB and University of Antwerp, Center for Molecular Neurology, Molecular Neurogenomics Group, Antwerp, Belgium; (2) University Hospital "Marqués de Valdecilla", Santander, Spain

OP3_8 GENETIC HETEROGENEITY OF MOTOR NEUROPATHIES

Boglarka Bansagi
(1) Bansagi B, (1) Griffin H, (2) Whittaker R, (3) Antoniadi T, (1) Evangelista T, (2) Miller J, (3) Greenslade M, (3) Forester N, (1) Duff J, (1) Bradshaw A, (4) Kleinle S, (1) Boczonadi V, (1) Steele H, (5) Ramesh V, (1,6) Franko E, (1) Pyle A, (1) Lochmüller H, (1,7) Chinnery PF, (1) Horvath R.(1) MRC Centre for Neuromuscular Diseases and John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, UK; (2) Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK; (3) Bristol Genetics Laboratory, Pathology Sciences, North Bristol NHS Trust, Southmead

Hospital, Bristol, UK; (4) Medical Genetic Center, Munich, Germany; (5) Department of Paediatric Neurology, Royal Victoria Infirmary, Newcastle upon Tyne Foundation Hospitals NHS Trust, Newcastle upon Tyne, UK; (6) Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK; (7) Department of Clinical Neurosciences, Cambridge Biomedical Campus, University of Cambridge, Cambridge, UK

OP3_9 A BREED-PREVALENT CANINE MODEL OF LATE ONSET PERIPHERAL NEUROPATHY

Susannah Sample

(1) Sample SJ, (2) Salamat S, (1) Muir P, (1) Hao Z, (1) Rylander H, (1) Eminaga S, (1) Barnes-Heller HL, (1) Binversie EE, (1) Baker LA, (1) Hoffman CL, (1) Piazza A, (1) Volstad NJ, (1) Hans EC, (1) Svaren J. (1) University of Wisconsin School of Veterinary Medicine, Madison, Wisconsin; (2) University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA

OP3_10 FUNCTIONAL IMPLICATIONS OF HAND IMPAIRMENT IN PEDIATRIC CHARCOT-MARIE-TOOTH

Timothy Estilow

(1) Estilow T, (1) Glanzman AM, (2) Burns J, (2) Cornett KMD, (2) Menezes MP, (3) Shy R, (4) Moroni I, (4) Foscan M, (4) Pagliano E, (4) Pareyson D, (5) Laura M, (6) Bhandari T, (6) Muntoni F, (5) Reilly MM, (7) Finkel RS, (8) Sowden J, (8) Eichinger K, (8) Herrmann DN, (9) Shy ME, (10) Yum SW and (11) Ramchandren S; on behalf of the Inherited Neuropathies Consortium 1The Children's Hospital of Philadelphia, Philadelphia, USA; 2University of Sydney & Children's Hospital at Westmead, Sydney, Australia; 3Carver College of Medicine, Department of Pediatrics, University of Iowa, Iowa City, USA; 4IRCCS Foundation, Carlo Besta Neurological Institute, Milan, Italy; 5MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, UK; 6UCL Institute of Child Health & Great Ormond Street Hospital, London, UK; 7Neuromuscular Program, Division of Neurology, Nemours Children's Hospital, Orlando, USA; 8Department of Neurology, University of Rochester, Rochester, NY, USA; 9 Carver College of Medicine, Department of Neurology, University of Iowa, Iowa City, USA; 11The Children's Hospital of Philadelphia, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, PA, USA 11Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA

OP3_11 DISEASE PROGRESSION IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: A LONGITUDINAL STUDY USING RASCH ANALYSIS-BASED WEIGHTED CMT NEUROPATHY SCORES

Vera Fridman

(1) Fridman V, (1) Sillau S., on behalf of the (2) Inherited Neuropathies Consortium (INC). (1) University of Colorado Hospital, Aurora, CO, USA, (2) University of Iowa Hospitals and Clinics, Iowa City, IA, USA

OP3_12 INTRATHECAL GENE THERAPY IN DIFFERENT MUTANT MOUSE MODELS OF CMT1X

Alexia Kagiava

(1) Kagiava A, (1) Karaiskos C, (2) Richter J, (2) Tryfonos C, (1) Lapathitis G, (1) Sargiannidou I, (2) Christodoulou C, (1, 3) Kleopa KA. (1) Neuroscience Laboratory, (2) Department of Molecular Virology and (3) Neurology Clinics, Cyprus School of Molecular Medicine, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus

OP3_13 ROLE OF X-BOX BINDING PROTEIN 1 (XBP1) IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1B

Thierry Touvier

(1) Touvier T, (1) Ferri C, (1) Mastrangelo R, (2,3) Glimcher L, (4,5,6) Wrabetz L, (1) D'Antonio M. (1) Myelin Biology Unit, Division of Genetics and Cell Biology, San Raffaele Scientific Institute, DIBIT, Milan, Italy, (2) Department of Cancer Immunology and Virology, Dana- Farber Cancer Institute, Boston, USA, (3) Department of Medicine, Harvard Medical School, Boston, USA, (4) Hunter James Kelly Research Institute and Departments of (5) Biochemistry and (6) Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, USA

OP3_14 RANDOMISED TRIAL OF PROGRESSIVE RESISTANCE EXERCISE FOR CHILDHOOD CHARCOT-MARIE-TOOTH DISEASE

Joshua Burns

(1,2) Burns J, (1) Sman AD, (1) Cornett KMD, (1,2) Wojciechowski E, (1) Walker T, (1,2) Menezes MP, (1) Mandarakas MR, (1,2) Rose KJ, (1,2) Bray P, (2) Sampaio H, (2,3) Farrar M, (1) Refshauge KM, (1) Raymond J for the FAST Study Group. (1) University of Sydney, New South Wales, Australia; (2) Sydney Children's Hospitals Network (Randwick and Westmead), New South Wales, Australia; (3) University of New South Wales, Sydney, Australia

OP3_15 NOCICEPTIN/ORPHANIN FQ OPIOID PEPTIDE (NOP) RECEPTOR EXPRESSION IN PACHYONYCHIA CONGENITA (PC)

Baohan Pan

(1) Baohan Pan, (2) Wolfgang Schröder, (2) Ruth Jostock, (3) Mary Schwartz, and (1) Michael Polydefkis (1) Department of Neurology, The Johns Hopkins University SOM, Baltimore, USA; (2) Translational Science & Intelligence (WS) and In-vitro Biology & Biomarker Research Unit (RJ), Grünenthal GmbH, Aachen, Germany; (3) Pachyonychia Congenita Project. Salt Lake City, USA

12.00 - 13.00 Sponsor Symposium 2: Kedrion AUDITORIUM

CHALLENGES IN NEUROPATHIES – WHAT IS THE NEXT?

12.00 Chair: **Eduardo Nobile Orazio** - Milan, Italy

12.05 Current research and open questions in GBS
Pieter van Doorn - Rotterdam, The Netherlands

12.20 Paranodal antibodies as predictor of response to IVIg in CIDP
Claudia Sommer - Würzburg, Germany

12.35 Experimental study on effectiveness of IVIg in bortezomib-induced peripheral neuropathy
Guido Cavaletti - Milan, Italy

12.50 Open Discussion (Q&A)

12.00 - 13.00 Sponsor Symposium 2: Pfizer TRAMUNTANA 1+2 ROOM

DRIVING CHANGE: NOVEL RESEARCH INTO EARLY SCREENING AND DIAGNOSIS OF HEREDITARY TRANSTHYRETIN AMYLOIDOSIS POLYNEUROPATHY

12.00 Screening of TTR mutations in a sample of patients with axonal polyneuropathy by melting curve analysis
Adriano Jimenez-Escrig - Spain

12.10 Biomarkers of small-fiber neuropathy in amyloid neuropathy
Sung-Tsang Hsieh - Taiwan

12.20 Cutaneous nerve measures in TTR-FAP
Michael Polydefkis - United States

12.30 Early skin denervation in transthyretin amyloid neuropathy
Mitsuharu Ueda - Japan

12.40 Prevalence of transthyretin-type cerebral amyloid angiopathy ATTR-FAP patients and its early diagnosis using PIB-PET Imaging
Yoshiki Sekijima - Japan

12.50 Q&A and Close
Adriano Jimenez-Escrig - Spain

12.00 - 14.00 **PNS Business Meeting** AUDITORIUM

13.00 - 14.30 **Poster Viewing** TRAMUNTANA FOYER

13.00 - 14.30 Lunch

Individual Meetings 2

14.30 - 19.00 Diabetic Neuropathy: Branching Out TRAMUNTANA 3

14.30 Welcome: It's Time to Branch-Out
Eva L. Feldman -Ann Arbor, United States

New Insights into Disease Pathogenesis
Chairs: **Douglas Zochodne** (University of Alberta, Edmonton) and **Anete Dudele** (Aarhus University)

14.40 Schwann Cells, Axons and Microvessels: The Trio of Diabetic Neuropathy
Nadia Goncalves - Aarhus, Denmark

15.00 Diabetic Neuropathy is a Disorder of Trafficking
Amy Rumora - Ann Arbor, United States

15.20 Bioenergetic Failure: The Crux of Diabetic Neuropathy
Lucy Hinder - Ann Arbor, United States

15.40 Nociceptor Excitability Underlies Axon Loss in Diabetic Neuropathy:
A New Disease Modifying Target
Daniela Maria Menichella - Chicago, United States

Innovations and Insights: Who Knew These Molecules Could Have a Role in Diabetic Neuropathy?
Chairs: **Nathan Staff** (Mayo Clinic, Rochester) and **Anna Grisold** (University of Vienna)

16.00 A Role for Unexplored Novel Sensory Neuron Proteins in Diabetic Neuropathy
Trevor Poitras - Edmonton, Canada

16.15 NADPH Oxidases: New Insights into the Molecular Pathogenesis of Diabetic Neuropathy
Stéphanie Eid - Beirut, Lebanon

16.30 Coffee

Metabolic Syndrome and Diabetic Neuropathy
Chairs: **Gordon Smith** (University of Utah) and **Phillipe O'Brien** (University of Michigan)

17.00 Phenotype the Prototype
Christopher Gibbons - Boston, United States

17.20 Fat is Where It's At
Brian Callaghan - Ann Arbor, United States

17.40 I Advise Exercise
Michael Cooper B.S. - Kansas, United States

Diabetic Neuropathy Consortium: Is Now the Time?

18.00 The Peripheral Neuropathy Research Registry
Ahmet Hoke - Baltimore, United States

18.10 Diagnostic Value of a Simple Symptom Score
Rens Hanewinckel - Rotterdam, The Netherlands

18.20 How We Started the Inflammatory Neuropathy Consortium:
Do's and Don'ts and Advice for the Future
Richard Hughes - London, United Kingdom

18.40 Panel Discussion: Diabetic Neuropathy Consortium—Has the Time Come?

14.30 - 18.30 Charcot-Marie-Tooth and Related Neuropathies (CMTR) AUDITORIUM

PLENARY 1
Presented by **Steve S. Scherer** (Philadelphia, United States)

14.30 Intrathecal gene delivery of GJB1 in animal models of CMTX1
Kleopas Kleopa - Nicosia, Cyprus

PLATFORM 1
Chairs: **Mary M. Reilly** and **Michael E. Shy**

15.00 GENOME-WIDE ASSOCIATION STUDY IDENTIFIES POTENTIAL GENETIC MODIFIERS IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A
Stephan Zuchner - Miami, United States

15.10 SCHWANN CELL-SPECIFIC DELETION OF THE ENDOSOMAL PI 3-KINASE VPS34 LEADS TO DELAYED RADIAL SORTING OF AXONS, ARRESTED MYELINATION, AND ABNORMAL ERBB2-ERBB3 TYROSINE KINASE SIGNALING
Fred Robinson - Portland, Oregon, United States

15.20 DISEASE PROGRESSION IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: A LONGITUDINAL STUDY USING RASCH ANALYSIS-BASED WEIGHTED CMT NEUROPATHY SCORES
Vera Fridman - Aurora, Colorado, United States

15.30 A KNOCK-IN / KNOCK-OUT MOUSE MODEL FOR SMALL HEAT SHOCK PROTEIN HSPB8 MIMICKING DISTAL HEREDITARY MOTOR NEUROPATHY AND MYOFIBRILLAR MYOPATHY
Vincent Timmerman - Antwerpen, Belgium

15.40 MUTATIONAL BURDEN ANALYSIS IN INHERITED PERIPHERAL NEUROPATHIES
Dana Bis - Miami, United States

15.50 DEVELOPMENT AND PILOT TESTING OF A FUNCTIONAL OUTCOME MEASURE FOR ADULTS WITH CHARCOT MARIE TOOTH NEUROPATHY (CMT-FOM)
David Herrmann- Rochester, United States

16.00 Break

PLENARY 2
Presented by **Davide Pareyson** - Milan, Italy

16.30 Rebalancing proteostasis as a therapeutic pproach in ER-stress related neuropathies
Maurizio D'Antonio - Milan, Italy

PLATFORM 2
Chairs: **Vincent Timmerman** and **Lawrence Wrabetz**

17.00 ACE-083, A LOCALLY-ACTING GDF/ACTIVIN LIGAND TRAP, AUGMENTS DORSIFLEXOR MUSCLE FUNCTION IN A MURINE MODEL OF CHARCOT-MARIE-TOOTH (CMT) DISEASE
Jia Li - Cambridge, United States

17.10 GENOMIC ANALYSIS REVEALS FREQUENT TRAF7 MUTATIONS IN INTRANEURAL PERINEURIOMAS
Michelle Mauermann - Rochester, United States

17.20 FUNCTIONAL VALIDATION OF NON-CODING VARIANTS OF GJB1 IN PATIENTS WITH CMTX1
Andrea Cortese - London, United Kingdom

17.30 A MULTICENTRE RETROSPECTIVE STUDY OF CHARCOT-MARIE-TOOTH DISEASE TYPE 4B (CMT4B)
Davide Pareyson - Milan, Italy

17.40 ROLE OF THE ALPHA SECRETASE TACE DURING WALLERIAN DEGENERATION
Marta Pellegatta - Milan, Italy

17.50 Late breaking news

18.00 **CMTR business**

14.30 - 18.00 Inflammatory Neuropathy Consortium TRAMUNTANA 1+2 ROOM

Short Talks and Oral Poster Presentations

14.30- 14.45 **GBS: Dilemmas in diagnosis and treatment**
Pieter van Doorn, **Bart Jacobs**

14.45 - 15.15 **Oral Poster Session 1 GBS**
Chairs: **Amy Davidson** and **Ruth Huizinga**

CHANGES OF SERUM IGG DIMER LEVELS AFTER TREATMENT WITH IVIG IN GUILLAIN-BARRÉ-SYNDROME
Martin K. R. Svačina

Ca(2+)-DEPENDENT ANTI-GANGLIOSIDE ANTIBODY IN SERONEGATIVE GUILLAIN-BARRÉ SYNDROME.
Ayumi Uchibori

THE CHALLENGES OF ACCURATE DIAGNOSIS OF ZIKA VIRUS ASSOCIATED GUILLAIN-BARRÉ SYNDROME (GBS) IN A DENGUE ENDEMIC AREA
Ohnmar Ohnmar

SMALL VOLUME PLASMA EXCHANGE FOR GUILLAIN-BARRE SYNDROME IN LOW INCOME COUNTRIES: A SAFETY AND FEASIBILITY STUDY
Badrul M Islam

GBS CLASSIFICATION ACCORDING TO TWO-SETS OF EMG EXAMINATIONS IN A SAMPLE OF THE BRAZILIAN POPULATION
Marques Júnior Wilson

EGOS DID NOT HAVE A GOOD CAPACITY TO PROGNOSIS IN GBS IN RIO GRANDE DO NORTE, BRAZIL
Mário Emílio Dourado

DOES INTRAVENOUS IMMUNOGLOBULIN SERVE AS AN EFFECTIVE TREATMENT FOR GUILLAIN-BARRÉ SYNDROME IN DEVELOPING COUNTRIES? A CONTROLLED MATCHED PAIR ANALYSIS
Nowshin Papri

QUANTITATIVE AUTONOMIC ASSESSMENT IN GUILLAIN-BARRÉ SYNDROME
Cheng-Yin Tan

CD1A AND CD1E GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH THE SUSCEPTIBILITY OF GUILLAIN-BARRÉ SYNDROME IN BANGLADESH
Zhahirul Islam

15.15 - 15.30 Paraproteinemic neuropathies and their treatment
Michelle Mauermann

15.30 - 16.10 **Oral Poster Session 2**
Paraproteinemic and related immune neuropathies
Chairs: **Chiara Briani** and **Yusuf Rajabally**

COMPARISON OF TWO-YEAR RESPONSE TO LENALIDOMIDE OR PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION IN PATIENTS WITH POEMS
Mariangela Bianco

THE FRANCOPHONE ANTI-MAG COHORT: ANALYSIS OF THERAPEUTIC MANAGEMENT IN 202 PATIENTS
Jean-Philippe Camdessanche

NEOD001 DEMONSTRATES DURABLE PERIPHERAL NEUROPATHY RESPONSES IN PATIENTS WITH LIGHT CHAIN AMYLOIDOSIS AND PERSISTENT ORGAN DYSFUNCTION: RESULTS FROM A PHASE 1/2 STUDY
Elena Alvarez-Baron

DO ANTI-MAG TITERS HAVE A GOOD CORRELATION WITH CLINICAL STATUS IN IgM ANTI-MAG NEUROPATHY?
Jean-Marc Léger

HEREDITARY OR INFLAMMATORY CHILDHOOD NEUROPATHY – ELECTROPHYSIOLOGICAL ABNORMALITIES HELPFUL IN THE DIFFERENTIATION
Anna Potulska-Chromik

THROMBOEMBOLIC EVENTS IN INFLAMMATORY NEUROPATHY PATIENTS ON IVIG
Aisling Carr

IMMUNE CHECKPOINT INHIBITOR-INDUCED ACUTE NEUROPATHIES
Thierry Kuntzer

SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF THE FCRN INHIBITOR UCB7665: A PHASE I STUDY
Peter Kiessling

ANTIBODIES AGAINST CELL ADHESION MOLECULES AND NEURAL STRUCTURES IN PARANEOPLASTIC NEUROPATHIES
Ana Maria Siles

CLINICAL AND ELETRODIAGNOSTIC FEATURES OF GANGLIONOPATHIES WITH SPECIAL REFERENCE TO ULNAR SENSORY-MOTOR AMPLITUDE RATIO (USMAR) FROM A TERTIARY CARE CENTER IN INDIA
Anjan Pyal

16.10 - 16.40 Break

16.40 - 17.10 **Oral Poster Session 3**

Basic Science in Immune Neuropathies

Chairs: **Simon Rinaldi** and **Helmar Lehmann**

THE CRYPTIC 68-104 REGION OF MYELIN BASIC PROTEIN (MBP) CAUSES PAIN FROM LIGHT TOUCH EXCLUSIVELY IN FEMALE RODENTS: AUTOIMMUNE MECHANISMS OF SEXUAL DIMORPHISM IN MECHANICAL ALLODYNIA
Veronica Shubayev

AUTOPHAGOLYSOSOME-MEDIATED MYELIN CORPSE FORMATION BY SCHWANN CELLS IN SEGMENTAL DEMYELINATION
Byeola Yoon

EFFICACY OF IMMUNOGLOBULINS FOR NOD B7-2 KO MICE
Masahiro Iijima

AUTOIMMUNE T CELLS IN AN EX VIVO MODEL OF THE PERIPHERAL NERVOUS SYSTEM
Anne Mausberg

CILOSTAZOL MODULATES SEQUENTIAL EXPRESSION OF MATRIX METALLOPROTEINASES AND THEIR INTRINSIC INHIBITOR WITHIN PERIPHERAL NERVOUS TISSUE DURING EXPERIMENTAL AUTOIMMUNE NEURITIS
Toshiki Fujioka

EFFECTIVE THERAPEUTIC EFFECT OF HUMAN IMMUNOGLOBUMIN AND A RECOMBINANT Fc PORTION ON A RAT MODEL FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)
Susana Brun

RABBIT ANTI-FGFR3 ANTIBODIES INDUCE NEURON CELL DEATH AND MODULATE FGFR3 AND NMDA AND AMPA RECEPTORS THROUGH THE P38-MAP KINASE PATHWAY
Jean-Christophe Antoine

17.10 - 17.30 Improving the diagnosis of CIDP: What should future guidelines look like?
Jeffrey Allen, Peter van den Bergh

17.30 - 18.00 **Oral Poster Session 4**

CIDP

Chairs: **Jeffrey Allen** and **Peter van den Bergh**

ULTRA HIGH FREQUENCY ULTRASOUND (UHFUS) NERVE IMAGING IN CIDP PATIENTS
Angela Puma

CAN NK CELLS HELP DISCRIMINATE IVIG TREATMENT RESPONSE IN PATIENTS WITH CIDP?
Anne K Mausberg

CLINICO-ELECTROPHYSIOLOGICAL CORRELATION WITH ANTI-NEUROFASCIN155 ANTIBODY LEVELS IN THE ANTIBODY-POSITIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY PATIENTS
Hidenori Ogata

INTRAVENOUS IMMUNOGLOBULIN THERAPY FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN PEDIATRIC PATIENTS: AN OBSERVATIONAL STUDY
Alphonse Hubsch

FREQUENCY, PROGRESSION AND THERAPY OF ATYPICAL CIDP: DATA FROM THE ITALIAN DATABASE ON CIDP
Pietro Emiliano Doneddu

RANDOMIZED CONTROLLED TRIAL OF ORAL FINGOLIMOD IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (FORCIDP TRIAL): SUBGROUP ANALYSES
Richard Hughes

CORTICOSTEROID TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY – A MULTICENTER, RETROSPECTIVE STUDY
Gwen Van Lieverloo

PREDICTIVE FACTORS OF LONG-TERM DISABILITY IN CIDP
Emanuele Spina

19.00 - 20.00 **Junior and New Members Reception** TRAMUNTANA HALL

19.00 - 20.00 Put up Posters for Poster Session 3 &
Oral Poster Presentations Sessions 4 - 5 TRAMUNTANA FOYER

Poster Session 2 TRAMUNTANA FOYER

P2_1 A QUALITY IMPROVEMENT STRATEGY:ULNAR NERVE CONDUCTION STUDY OF THE FIRST DORSAL INTEROSSEOUS MUSCLE
Elie Naddaf
Anandan C, Litchy WJ, Laughlin RS, Leep Hunderfund AN, Naddaf E. Mayo Clinic, Rochester, USA

P2_2 PAIN AND ANXIETY WITH ELECTRODIAGNOSTIC PROCEDURES
Mamatha Pasnoor
Pasnoor M, Veerapaneni K, Murphy R, Statland JM, Kimple D, Hamasaki A, Glenn MD, Herbelin L, Barohn RJ, Jawdat O, Dimachkie MM. The Univeristy of Kansas Medical Center, Kansas City, KS, USA

P2_3 THE APPLICABILITY OF CORNEAL CONFOCAL MICROSCOPY IN SMALL FIBER NEUROPATHY
Maurice Sopacua
(1) Sopacua M, (1) Hoeijmakers JGJ, (1) Dickman MM, (1) Nuijts RMMA, (2) Merkies ISJ, (1) Faber CG. (1) Maastricht University Medical Center, Maastricht, the Netherlands; (2) St. Elisabeth Hospital, Willemstad, Curaçao

P2_4 DULOXETINE IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY
Roser Velasco Fargas
(1,2) Velasco R, (1) Besora S, (3) Santos C, (1) Sala R, (1) Izquierdo C, (1) Simó M, (1,3) Gil-Gil M, (3) Jiménez L, (3) Pardo B, (3) Calvo M, (3) Palmero R, (4) Clapés V, (1,2) Bruna J. (1) Neuro-Oncology Unit, Department of Neurology, University Hospital of Bellvitge- Catalan Institute of Oncology, L´Hospitalet, Barcelona, Spain. (2) Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain. (3) Department of Medical Oncology, Hospital Duran i Reynals, Catalan Institute of Oncology, L´Hospitalet, Barcelona, Spain. (4) Department of Clinical Hematology, Hospital Duran i Reynals, Catalan Institute of Oncology, L´Hospitalet, Barcelona, Spain

P2_5 CHANGES IN PAIN THRESHOLD BY SKIN TEMPERATURE: A STUDY BY INTRAEPIDERMAL ELECTRICAL STIMULATION
Chieko Suzuki
Suzuki C, Baba M, Kon T, Funamizu Y, Ueno T, Haga R, Nishijima H, Arai A, Nunomura J, Tomiyama M. Department of Neurology, Aomori Prefectural Central Hospital, Aomori, Japan

P2_6 STRESS-INDUCED MECHANICAL ALLODYNIA, BLADDER HYPERSENSITIVITY, AND ANHEDONIA IN AN ANXIETY- PRONE MOUSE STRAIN
Pau Yen Wu
Wu PY, Yang X, Christianson JA,Wright DE. University of Kansas Medical Center, Kansas City, USA

P2_7 NOSOCOMIAL TREATMENT-INDUCED NEUROPATHY OF DIABETES MELLITUS (TIND)?
Benjamin Jun Hwee Lee
(1) Lee BJH, (2) Ohnmar O., (1) Wong J, (2) Koh SJ, (2) T. Umapathi. (1) Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore (2) National Neuroscience Institute, Singapore

P2_8 THE AXONAL PROPERTIES IN PREDIABETIC PATIENTS
Yi-Chen Lin
(1) Lin Y. (2) Sung J. (3) Chang T. (4) Jowy T. (1) Department of Neurology, Taipei Municipal Wanfang Hospital, Taipei, Taiwan; (2) Department of Neurology, Taipei Municipal Wanfang Hospital, Taipei, Taiwan; (3) Department of Neurology, Taipei Municipal Wanfang Hospital, Taipei, Taiwan; (4) Department of Neurology, Taipei Municipal Wanfang Hospital, Taipei, Taiwan

P2_9 AUTONOMIC NERVE FIBER INVOLVEMENT IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Ying Liu
Liu Y, Liu B, Sebastian B, Wozniak KM, Wu Y, Slusher B, Polydefkis M. Johns Hopkins School of Medicine, Baltimore, USA

P2_10 ADIPOSE-NERVE SIGNALING IN PERIPHERAL NEUROPATHY

Faye Mendelson
Hinder LM, Mendelson F, Backus C, Feldman EL. University of Michigan, Ann Arbor, MI, USA

P2_11 THE RELATIONSHIP BETWEEN CENTRAL AORTIC SYSTOLIC PRESSURE AND PERIPHERAL BLOOD PRESSURE IN PATIENTS WITH POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

Brandon Ng
(1) Ng CJB, (2) Ng JPH; (3) Tay LB, T, (3) Umapathi. (1) Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; (2) Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; (3) National Neuroscience Institute, Singapore, Singapore

P2_12 VENTRAL ABDOMINAL SENSORY LOSS IS COMMON IN LENGTH DEPENDENT SENSORIMOTOR PERIPHERAL NEUROPATHY

Benn E. Smith
Gervais CBL, Ross MA, Goodman BP, Khoury JA, Muzyka I, Smith BE. Mayo Clinic in Arizona, Scottsdale, AZ, USA

P2_13 HIGH FAT FED FEMALE MICE DEVELOP PERIPHERAL NEUROPATHY DESPITE NORMAL SYSTEMIC INSULIN SIGNALING

Phillipe O'Brien
Hayes JM, O'Brien PD, Backus C, and Feldman EL. Department of Neurology, University of Michigan, Michigan, USA

P2_14 SENSORY AXONAL DYSFUNCTION IN THE PAINFUL DIABETIC POLYNEUROPATHY

Tsui-san Chang
(1) Chang TS, (1,2) Lin CS, (3,4) Tani J, (1,4) Sung JY. (1) School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; (2) University of New South Wales, Sydney, Australia; (3) Taipei Medical University and National Health Research Institutes, Taipei, Taiwan; (4) Wan Fang Hospital, Taipei, Taiwan

P2_15 STRUCTURAL AND FUNCTIONAL TESTS OF NEUROPATHY IN DIABETES

Christopher Gibbons
Gibbons C, Garcia J, Casasola M, Freeman R. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

P2_16 SENSORY SMALL FIBERS IMPLICATION ON INFLAMMATION REGULATION DURING SKIN PRESSURE ULCER DEVELOPMENT IN MICE

Flavien Bessaguet
(1) Bessaguet F, (1) Sturtz F, (1,2) Magy L, (1) Desmouliere A, (1) Bourthoumieu S and (1) Demiot C. (1) EA 6309 - Myelin Maintenance & Peripheral Neuropathy, Faculties of Medicine and Pharmacy, University of Limoges, Limoges, France; (2) Department of Neurology, Reference Center for Rare Peripheral Neuropathies, University Hospital of Limoges, Limoges, France

P2_17 EFFECTS OF MONASTROL IN BORTEZOMIB INDUCED PERIPHERAL NEUROPATHY

Ilja Bobylev
(1, 2) Bobylev I, (3) Peters D, (4) Vyas M, (2) Barham M, (1, 2) Klein I, (4) von Strandmann EP, (2) Neiss WF, (1, 2) Lehmann HC. (1) University Hospital of Cologne, Cologne, Germany; (2) University of Cologne, Cologne, Germany; (3) University of Düsseldorf, Düsseldorf, Germany; (4) Philipps University, Marburg, Germany

P2_18 DEXAMETHASONE REDUCES THE FOREING BODY RESPONSE TO PARYLENE-C INTRANEURAL IMPLANTS IN RATS

Natalia de la Oliva
De la Oliva N, Del Valle J, Navarro X. Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain

P2_20 ULNAR NERVE ENTRAPMENT IN MASSIVE MUSCLE FIBROSIS FOLLOWING INTRAMUSCULAR ANABOLIC STEROID INJECTIONS: A CASE REPORT

Vivian Drory
(1) Fainmesser Y, (2,3) Dori A, (1,3) Drory VE (1) Department of Neurology and Neuromuscular Service, Tel-Aviv Medical Center, Tel-Aviv, Israel; (2) Department of Neurology, Sheba Medical Center, Ramat Gan, Israel; (3) Sackler Faculty of Medicine, Tel Aviv University, Israel

P2_21 ENRICHEMENT OF CHITOSAN TUBES WITH SKELETAL MUSCLE FIBRES TO IMPROVE PERIPHERAL NERVE REGENERATION

Giovanna Gambarotta
(1,2) Fornasari BE, (1,2) Raimondo S, (1,2) Ronchi G, (3) Crosio A, (1) Budau CA, (1) El Soury M, (1,2) Muratori L, (4) Tos P, (3) Battiston B, (1,2) Geuna S, (1) Gambarotta G. (1) Department of Clinical and Biological Sciences, University of Torino, Italy; (2) Neuroscience Institute Cavalieri Ottolenghi, Torino, Italy; (3) Microsurgery Unit, Health and Science City, CTO, Torino, Italy; (4) Hand Microsurgery and Surgery, Gaetano Pini Hospital, Milano, Italy

P2_22 THE MODIFIED MULTIPLE POINT STIMULATION METHOD FOR MOTOR NUMBER UNIT ESTIMATION

Akiko Hachisuka
(1, 2) Hachisuka A, (3) Senger J, (3) Curran M, (1, 3) Chan K.M. (1) Division of Physical Medicine and Rehabilitation, University of Alberta, Edmonton, Canada; (2) Department of Rehabilitation and Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; (3) Division of Plastic surgery, University of Alberta, Edmonton, Canada

P2_23 THE USE OF MAGNETIC RESONANCE NEUROGRAPHY IN PERIPHERAL NERVE SHEATH TUMORS

Megan Jack
Jack MM, Shah K, Everist B, Reyna J, Hylton P. The University of Kansas Medical Center, Kansas City, USA

P2_24 CRITICAL FACTORS AFFECTING FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY

Stefania Raimondo
(1,2) Morano M, (1) Gambarotta G, (1,2) Ronchi G, (3) Cillino M, (1,2) Fornasari BE, (1,2) Fregnan F, (4) Tos P, (3) Cordova A, (3) Moschella F, (1,2) Geuna S, (1,2) Raimondo S. (1) Department of Clinical and Biological Sciences, University of Torino, Orbassano (TO), Italy; (2) Neuroscience Institute of the "Cavalieri Ottolenghi" Foundation (NICO), University of Torino, Orbassano (TO), Italy; (3) Plastic and Reconstructive Surgery. Department of Surgical, Oncological and Oral Sciences, University of Palermo, Palermo, Italy; (4) Hand Microsurgery and Surgery, Gaetano Pini Hospital, Milano, Italy

P2_25 EFFECT OF NİFEDİPİNE ON SURGICALLY ANASTOMIZED PERIPHERAL NERVE REGENERATION

Özgür Demir
(1) Demir Ö., (2) Yazıcı T. Affiliations: (1) University of Gaziosmanpaşa School of Medicine, Neurosurgery, Tokat, Turkey, (2) Kent Hospital, Neurosurgery, Giresun, Turkey

P2_26 NEPRILYSIN IS NOT INVOLVED IN REGENERATION AND RE-MYELINATION AFTER NERVE INJURY

Ilaria Cervellini
(1) Cervellini I, (1) Galino J, (1) Zhu N, (2) Bao Lu, (1) Bennett DL. (1) NDCN, University of Oxford, Oxford, UK; (2) Harvard Medical School, Boston, Massachusetts

P2_27 LYSOPHOSPHATIDIC ACID CONTRIBUTES TO A SCHWANN CELL PHENOTYPE ASSOCIATED WITH PERIPHERAL NERVE INJURY

Fabian Szepanowski
(1) Szepanowski F, (1) Szepanowski LP, (1) Kleinschnitz C, (2) Kieseier BC, (1) Stettner M. (1) Department of Neurology, Medical Faculty, University Duisburg-Essen, Essen, Germany. (2) Department of Neurology, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

P2_28 VECTOR-BORNE VIRAL INFECTIONS IN GUILLAIN BARRE SYNDROME PATIENTS

Serhat Okar
(1) Okar SV, (2) Ergunay K, (1,3) Bekircan-Kurt CE, (1,3) Erdem-Ozdamar S, (1,3) Tan E. Hacettepe University (1) Department of Neurology, (2) Virology Unit, Department of Medical Microbiology, (3) Neuromuscular Disease Research Laboratory Ankara Turkey

P2_29 QUALITY OF LIFE IN ANTI-MAG NEUROPATHY: EVALUATION OF DETERMINANTS IN A MULTICENTRE EUROPEAN SETTING

Hiew Fu Liong
(1) Fu Liong H, (2) Aude-Marie G, (3) Anne-Catherine AN, (4) Emilien D, (5) Julien C, (6) Shahram A, (7) Yusuf R. (1) Regional Neuromuscular Clinic, Queen Elizabeth Hospital, University Hospitals of Birmingham, Birmingham, U.K; (2) Referral Centre for Neuromuscular Diseases and ALS, university hospital La Timone, 264 rue Saint-Pierre, 13005, Marseille, France; (3) Centre de Référence Maladies Neuromusculaires de l'Enfant et de l'Adulte Nantes-Angers, Centre Hospitalier Universitaire d'Angers, Angers, France; (4) Referral Centre for Neuromuscular Diseases and ALS, university hospital La Timone, 264 rue Saint-Pierre, 13005, Marseille, France, Aix-Marseille University, CNR2M, CNRS UMR 7286, Medicine Faculty, Marseille, France; (5) Centre de Référence Maladies Neuromusculaires de l'Enfant et de l'Adulte Nantes-Angers, Centre Hospitalier Universitaire d'Angers, Angers, France; (6) Referral Centre for Neuromuscular Diseases and ALS, university hospital La Timone, 264 rue Saint-Pierre, 13005, Marseille, France, Aix Marseille University - Inserm UMR S 910 Medical Genetics and Functional Genomics, Marseille, France; (7) Regional Neuromuscular Clinic, Queen Elizabeth Hospital, University Hospitals of Birmingham, Birmingham, U.K, School of Life and Health Sciences, Aston Brain Centre, Aston University, Birmingham, U.K

P2_30 SENSORY AXON EXCITABILITY IN MULTIFOCAL MOTOR NEUROPATHY

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P2_31 ANTI-A DONOR SCREENING AND THE RISK OF HEMOLYTIC ANEMIA WITH HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN TREATMENT – A HOSPITAL-BASED COHORT STUDY IN THE US

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P2_32 DE-NOVO SUBCUTANEOUS IMMUNOGLOBULIN G FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. A SINGLE CENTRE EXPERIENCE OF 3 PATIENTS

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P2_35 SWITCHING FROM IVIG TO FLEXIBLY-DOSED SCIG IN PATIENTS WITH CIDP AND MMN: CLINICAL AND PATIENT EXPERIENCE

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P2_36 AN UP-TO-DATE REVIEW ON SWEATING DISTURBANCES IN GUILLAIN-BARRÉ SYNDROME

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P2_37 SENSORY GUILLAIN BARRE SYNDROME

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P2_38 DIFFERENTIATION POEMS AND CIDP BY TERMINAL LATENCY INDEX

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P2_39 FIRST GLOBAL MULTIFOCAL MOTOR NEUROPATHY (MMN) QUALITY OF LIFE (QOL) PATIENT SURVEY IDENTIFIES NEEDS IN EDUCATION AND TREATMENT

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P2_40 INTRAVENOUS IMMUNOGLOBULIN (IVIG) TREATMENT-RELATED FLUCTUATIONS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) PATIENTS USING DAILY GRIP STRENGTH MEASUREMENTS (GRIPPER): STUDY DESIGN AND PROGRESS UPDATE

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P2_41 INFLAMMATORY POLYRADICULOPATHY ASSOCIATED WITH SJOGREN'S SYNDROME

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P2_42 FOLLOW-UP STUDY OF NERVE ULTRASOUND IN A PATIENT WITH PRIMARY NEUROLYMPHOMATOSIS

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P2_43 A CURIOUS CASE OF NUMBNESS, DIZZINESS, WETNESS, and DRYNESS – IS ROSS SYNDROME ON THE SPECTRUM OF SJOGREN NEUROPATHY?

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P2_44 PATTERN OF PERIPHERAL NEUROPATHY IN SJOGREN'S SYNDROME IN A TERTIARY CARE HOSPITAL FROM SOUTH INDIA

Anjan Pyal
Sireesha Y, Meena A.K*, Pyal A, Sandeep G,Megha S U,Mridula K.R, Jabeen S.A, Varaprasad R, Liza R, Neeharika M.L,Rupam B. Nizam's
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P2_45 PERIPHERAL NERVE INVOLVEMENT IN CELIAC DISEASE: A NOVEL ASSOCIATION WITH A MULTIFOCAL ACQUIRED MOTOR AXONOPATHY (MAMA)

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P2_48 ACUTE TRANSIENT POLYNEURITIS ASSOCIATED WITH ZIKA VIRUS INFECTION

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P2_49 A DESCRIPTION OF GUILLAIN-BARRÉ SYNDROME IN LAOS PEOPLE DEMOCRATIC REPUBLIC

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P2_50 OCTAGAM® FOR NEUROLOGICAL DISORDERS: FOCUS ON CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY – DATA FROM 3 OBSERVATIONAL STUDIES

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P2_51 SONOGRAPHIC NERVE ENLARGEMENT IN SARCOID PERIPHERAL NEUROPATHY - A CASE REPORT -

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P2_52 EFFICACY OF CYCLOPHOSPHAMIDE IN ANTI-CONTACTIN-1 ANTIBODIES ASSOCIATED TO CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY AND MEMBRANOUS GLOMERULONEPHRITIS: A CASE REPORT

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P2_53 ATYPICAL MULTIFOCAL MOTOR NEUROPATHY WITH SCAPULAR WINGING

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P2_55 EPIDEMIOLOGY OF GUILLAIN-BARRÉ SYNDROME IN DENMARK – THE INTERNATIONAL GBS OUTCOME STUDY IN A POPULATION BASED PERSPECTIVE

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P2_56 OVERALL DISEASE IMPACT OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

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P2_57 PREVALENCE OF ANTI-NEUROFASCIN-155, ANTI-CONTACTIN-1 AND CONTACTIN-ASSOCIATED PROTEIN 1 ANTIBODIES IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: A SEROLOGICAL MULTICENTER STUDY IN ITALY

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P2_58 EFFICACY AND SAFETY OF THREE DIFFERENT DOSAGES OF IVIG (PANZYGA®) IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLY(RADICULO)NEUROPATHY (ProCID STUDY) – DESIGN OF A PHASE 3 STUDY

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P2_59 CONDUCTION BLOCKS AND PARESIS INDUCED BY PASSIVE TRANSFER OF ANTI-CONTACTIN-1 IGG OF PATIENTS WITH CIDP

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P2_60 ANTI-GANGLIOSIDE COMPLEX ANTIBODIES IN CHRONIC IMMUNE-MEDIATED NEUROPATHIES

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P2_61 SELECTIVE IN VIVO REMOVAL OF PATHOGENIC ANTI-MAG AUTOANTIBODIES - A NOVEL TREATMENT OPTION FOR ANTI-MAG NEUROPATHY

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P2_62 GUILLAIN-BARRÉ SYNDROME IN BANGLADESH: PAST, PRESENT AND FUTURE PERSPECTIVE

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P2_63 IMPROVING REVIEW PROCESSES FOR IVIG THERAPY: GETTING TO KNOW OUR AUNTS (AUSPICOUSLY UNINTERPRETABLE NOTE TAKING) AND UNCLES (UNCERTAIN NEUROLOGICAL CLINICAL ENTITIES)

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P2_64 ANTI-NFASC155 NEUROPATHY: A RELAPSING-REMITTING NEUROPATHY?

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P2_65 CD1A AND CD1E GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH THE SUSCEPTIBILITY OF GUILLAIN– BARRÉ SYNDROME IN BANGLADESH

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P2_66 CLONICAL SYMPTOMS OF SUBACUTE MYELO-OPTICO NEUROPATHY ARE ELOCITED BY MYELOPATHY RATHER THAN PERIPHERAL NEUROPATHY Matsumoto A 1

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P2_67 DO ANTI-MAG TITERS HAVE A GOOD CORRELATION WITH CLINICAL STATUS IN IgM ANTI-MAG NEUROPATHY?

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P2_68 MONTH OF BIRTH AS A RISK FACTOR FOR GUILLAIN-BARRÉ SYNDROME

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P2_69 FLAVIVIRUS ASSOCIATED GUILLAIN-BARRÉ SYNDROME IN SINGAPORE

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P2_70 A PEDIATRIC SERIES OF GUILLAIN BARRÉ SYNDROME INCLUDED IN IGOS PROTOCOL. ARGENTINIAN EXPERIENCE

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P2_71 PREDICTIVE FACTORS OF LONG-TERM DISABILITY IN CIDP

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P2_72 QUANTITATIVE AUTONOMIC ASSESSMENT IN GUILLAIN-BARRÉ SYNDROME

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P2_73 LYSOPHOSPHATIDYLCHOLINE - INDUCED ACUTE DEMYELINATION AGGRAVATES MOTOR AXON DYSFUNCTION IN A MOUSE MODEL OF CMT1B

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P2_74 SCO2 MUTATIONS CAUSE AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE

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P2_75 AMINOACYL tRNA SYNTHETASE GENE MUTATIONS INCLUDING GARS, MARS AND YARS GENES IN KOREAN PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE

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P2_76 SPINOBULBAR MUSCULAR ATROPHY COMBINED WITH CHARCOT-MARIE-TOOTH DISEASE: "DOUBLE TROUBLE" IN NEUROMUSCULAR DISORDERS

Kyomin Choi
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P2_77 AXONAL CMT WITH ATYPICAL PROXIMAL WEAKNESS CAUSED BY TRANSLATIONAL ELONGATION OF THE 3' UTR IN NEFH

Ki Wha Chung
(1) Nam DE, (2) Jung S-C, (3) Choi B-O, (1) Chung KW, (1) Kongju National University, Gongju, Korea; (2) Ewha Womans University School of Medicine, Seoul, Korea; (3) Sungkyunkwan University School of Medicine, Seoul, Korea

P2_78 COWCHOCK SYNDROME, 2 FAMILIAL CASES WITH A NEW MUTATION IN AIFM1 GENE

Gerardo Jose Cruz Velasquez
(1) Cruz-Velásquez GJ, (2) Miramar-Gallart MD, (1) Alarcia-Alejos R, (1) Roche-Bueno JC, (2) Rodríguez-Valle A, (1) Capablo-Liesa JL. (1) University Hospital Miguel Servet, Neurology Service, Zaragoza, Spain; (2) University Hospital Miguel Servet, Genetics Unit-Clinical Biochemistry Service, Zaragoza, Spain

P2_79 CHARCOT-MARIE-TOOTH 2W. A NEW MUTATION?

Marcos de Freitas
(1) de Freitas M, (1) Dias J, (1) Vidal C, (1) Szklarz D, (1) Nascimento O, (2) Kok F (1) Federal Fluminense University, Niterói, Brazil, (2) São Paulo University, São Paulo, Brazil

P2_80 GENOTYPIC AND PHENOTYPIC PRESENTATION OF TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY (TTR-FAP) IN TURKEY

Hacer Durmus
(1) Durmuş H, (1) Çakar A, (1) Sahin E, (2) Matur Z, (3) Poda M, (4) Altunoğlu U, (1) Oflazer-Serdaroğlu P, (1) Deymeer F, (1) Parman Y. (1) Istanbul University, Istanbul Medical Faculty, Neurology Department, Istanbul, Turkey; (2) Istanbul Bilim University, Medical Faculty, Neurology Department, Istanbul, Turkey; (3) Istanbul University, Genetics Department, Institute of Experimental Medical Research; (4) Istanbul University, Istanbul Medical Faculty, Department of Medical Genetics, Istanbul, Turkey

P2_81 SENSITIVITY TO CHANGE OF THE CHARCOT-MARIE-TOOTH NEUROPATHY SCORE (CMTNS) AND OVERALL NEUROPATHY LIMITATION SCALE (ONLS) IN A DATABASE OF FRENCH PATIENTS WITH CMT1A

Mickael Guedj
(1) Foucquier J, (1) Bertrand V, (2) Jouve E, (2) Truillet R, (1) Mandel J, (1) Laffaire J, (2) Blin O, (3) Magy L, (4, 5) Lehert P, (1) Hajj R, (1) Guedj M, (1) Cohen D and (2) Attarian S. (1) Pharnext, Issy-Les-Moulineaux, France; (2) Aix Marseille Université, APHM, Marseille, France; (3) Hôpital Dupuytren, Limoges, France; (4) University of Melbourne, Melbourne VIC 3010, Australia; (5) Faculty of Economics, Louvain, Belgium

P2_82 CHARCOT-MARIE-TOOTH DISEASE: GENETIC SUBTYPES IN NORTHWESTERN SPAIN

Tania García-Sobrino
(1 2) García-Sobrino T, (2 3) Blanco-Arias Patricia, (4) Vidal-Lijó M.P, (2 3)Quintáns Bea, (2 3)Sobrido MJ, (1 2) Pardo J. (1) Department of Neurology, Hospital Clínico, Santiago de Compostela, Spain; (2) Neurogenetics Research Group, Instituto de Investigaciones Sanitarias (IDIS), Santiago de Compostela, Spain; (3) Genomic Medicine Group (U711), Centre for Biomedical Network Research on Rare Diseases (CIBERER), Spain; (4) Department of Neurophysiology, Hospital Clínico, Santiago de Compostela. Spain

P2_83 GENE THERAPY ON RATS MODELS OF THE PERIPHERAL NEUROPATHY CHARCOT-MARIE-TOOTH

Helene Hajjar
(1) Hajjar H, (1) Gautier B, (1) Berthelot J, (1) Gonzalez E, (2) Gess B, (2) Young P (1) Tricaud N. (1) Institute of Neurosciences of Montpelllier, INSERM, University of Montpellier, Montpellier, France; (2) Universitätsklinikum Münster, Klinik für Schlafmedizin und neuromuskuläre Erkrankungen, Münster, Germany

P2_84 CHARCOT MARIE TOOTH DISEASE TYPE 4C: NOVEL MUTATIONS, CLINICAL PRESENTATIONS, AND DIAGNOSTIC CHALLENGES OF AN ATYPICAL CMT

Nivedita Jerath
(1) Jerath NU,(2) Mankodi A, (3) Crawford TO,(2) Grunseich C,(4) Baloui H, (2) Nnamdi-Emeratom C,(2) Schindler AB,(5) Heiman-Patterson T,(4) Chrast R,(1) Shy ME. (1) Department of Neurology, University of Iowa Carver College of Medicine, Iowa City, IA, USA; (2) Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA; (3) Department of Pediatric Neurology, Johns Hopkins University, Baltimore, MD, USA; (4) Department of Neuroscience and Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; (5) Department of Neurology, Drexel University College of Medicine, Philadelphia, PA, USA

P2_85 DIAGNOSTIC CHALLENGES IN THE MOLECULAR DIAGNOSIS OF CMT IN THE ERA OF NEXT GENERATION SEQUENCING (NGS)

Andrea Cortese
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P2_87 REDUCED INTRAEPIDERMAL NERVE FIBER DENSITY IN PATIENTS WITH REM SLEEP BEHAVIOUR DISORDER

Istvan Katona
(1) Katona I, (2) Schrempf W, (3,4) Dogan I, (5) von Felbert V, (2) Wienecke M, (3,4) Heller J, (3) Maier A, (2,6) Hermann A, (2) Linse K, (2) Brandt MD, (2) Reichmann H, (3,4,7) Schulz JB, (3) Schiefer J, (8) Oertel WH, (2,6,9,10) Storch A, (1) Weis J, (3,4,7) Reetz K. (1) Institute of Neuropathology, RWTH Aachen University, Aachen, Germany; (2) Department of Neurology, Technische Universität Dresden, Dresden, Germany; (3) Department of Neurology, RWTH Aachen University, Aachen, Germany; (4) JARA – Translational Brain Medicine, Jülich and Aachen, Germany; (5) Department of Dermatology and Allergology, RWTH Aachen University, Aachen, Germany; (6) German Center for Neurodegenerative Diseases (DZNE) Dresden, Dresden, Germany; (7) Institute of Neuroscience and Medicine (INM-11), Research Center Jülich GmbH, Jülich, Germany; (8) Department of Neurology, Philipps University Marburg, Germany; (9) Division of Neurodegenerative Diseases, Department of Neurology, Technische Universität Dresden,, Germany; (10) Department of Neurology, University of Rostock, Rostock, Germany

P2_88 SURGICAL MANAGEMENT OF FOOT AND ANKLE DEFORMITIES IN CHARCOT MARIE TOOTH DISEASE: RESULTS OF A PROSPECTIVE STUDY

Matilde Laurá
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P2_89 A RARE CASE OF NEUROFIBROMATOSIS PRESENTING WITH DEMYELINATING POLYNEUROPATHY

Hyung-Soo Lee
(1) Lee H-S, (2) Kim SM. (1) Presbyterian Medical Center, Jeonju, Korea; (2) Yonsei University College of Medicine, Seoul, Korea

P2_90 ENHANCEMENTS TO THE RARE DISEASES CLINICAL RESEARCH NETWORK CONTACT REGISTRY FOR THE INHERITED NEUROPATHIES CONSORTIUM

Devon Marking
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P2_91 A MPZ R98C CMT PATIENT PRESENTING A FLUCTUATING NEUROPATHY SUSCEPTIBLE TO TREATMENT

Wilson Marques Júnior
Germano CSB, Onofre PTBN, Bordini EC, Gouvea S, Barreira AA, Marques W Jr. Division of Neuromuscular Diseases, Department of Neurosciences and Behaviour Sciences, Clinical Hospital of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

P2_92 A NEW SYT2 MUTATION CAUSING PRESYNAPTIC NEUROMUSCULAR JUNCTION DYSFUNCTION AND DISTAL MOTOR NEUROPATHY (LEMS-CMT)

Nataly Montes-Chinea
(1) Montes-Chinea, NI, (1) Coutts, M, (1) Vidal C, (2) Courel, S, (2) Rebelo A, (2) Abreu L, (2) Zuchner S, (1,2) Saporta, MA. (1) Department of Neurology, University of Miami, Miami, USA, (2) Department of Human Genetics, University of Miami, Miami, USA

P2_93 CLINICAL AND PATHOLOGICAL FINDINGS IN FAMILIAL AMYLOIDOTIC POLYNEUROPATHY DUE TO TRANSTHYRETIN E61K

Tatsufumi Murakami
(1) Murakami T, (2) Nishimura H, (1) Nagai T, (1) Hemmi S, (1) Kutoku Y, (1) Sunada Y. (1) Department of Neurology, and (2) Department of Pathology, Kawasaki Medical School, Kurashiki, Japan

P2_94 PREGNANCY, SLEEP, FATIGUE AND OTHER ITEMS IN CHARCOT-MARIE-TOOTH DISEASE: DATA FROM QUESTIONNAIRES LINKED TO THE ITALIAN CMT NATIONAL REGISTRY

Davide Pareyson

(1) Pareyson D, (1) Calabrese D, (2) Santoro L, (2) Manganelli F, (3) Fabrizi GM, (4) Schenone A, (3) Cavallaro T, (4) Ursino G, (5) Previtali S, (6) Allegri I, (7,8) Padua L, (8) Pazzaglia C, (9) Quattrone A, (1) Villani F, (1) Pisciotta C, (10) Mazzeo A, (10) Vita G; for the Italian CMT Network. (1) IRCCS Foundation, "C. Besta" Neurological Institute, Milan; (2) Federico II University, Department of Neurosciences, Reproductive Sciences and Odontostomatology, Naples; (3) University of Verona, Department of Neurological, Biomedical and Motor Sciences, Verona; (4) University of Genoa, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal Infantile Sciences, Genoa; (5) Ospedale San Raffaele, Vita Salute San Raffaele University, Department of Neurology and INSPE, Milan; (6) A.O. di Parma, U.O. Neurologia, Parma; (7) Università Cattolica del Sacro Cuore, Rome; (8) Don Carlo Gnocchi Onlus Foundation, Department of Neuroscience, Milan; (9) Magna Graecia University, Department of Medical Sciences, Catanzaro; (10) University of Messina, Unit of Neurology, Department of Clinical and Experimental Medicine, Messina; Italy

P2_95 CLINICAL AND GENETIC HETEROGENEITY IN CHARCOT-MARIE-TOOTH NEUROPATHY TYPE 2 PATIENTS FROM TURKEY

Yesim Parman

1) Parman Y, (1) Durmus H, (1) Deymeer F, (1) Oflazer-Serdaroğlu P, (2) Battaloglu E. (1) Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey. (2) Bogazici University, Istanbul, Turkey

P2_96 ARL6IP1 CAUSES CONGENITAL INSENSITIVITY TO PAIN, SELF-MUTILATION AND SPASTIC PARAPLEGIA

Yann Pereon

(1) Péréon Y, (2) Nizon M, (2) Küry S, (2) Besnard T, (2) Quinquis D, (2) Boisseau P, (1) Magot A, (1) Mussini JP, (3) Mayrargue E, (4) Barbarot S, (2) Bézieau S, (2) Isidor B. (1) Reference Centre for Neuromuscular Disorders (2) Dept. of Genetics (3) Dept. of Paediatric Surgery (4) Dept. of Dermatology, University Hospital, Nantes France

P2_97 DETERMINING THE PATHOGENICITY OF NEWLY IDENTIFIED ATP7A VARIANTS USING PRIMARY FIBROBLASTS

Gonzalo Perez Siles

(1,2) Perez-Siles G, (1,2) Drew A, (1) Ellis M, (1) Kidambi M, (4) Takata R I, (4) Speck-Martins C E, (5) Hagerman K A, (5) Siskind C E, (5) Day J W, (6) Ginzberg M, (1,2,3) Nicholson G, (1,2,3) Kennerson M L. (1) Northcott Neuroscience Laboratory, ANZAC Research Institute, Sydney, Australia; (2) Sydney Medical School, University of Sydney, Sydney, Australia; (3) Molecular Medicine Laboratory, Concord Repatriation General Hospital, Sydney, Australia; (4) Sarah Network Rehabilitation Hospitals, Brasilia, DF, Brazil; (5) Department of Neurology, Stanford Health Care, Stanford, CA, USA; (6) Pediatric Neuromuscular Unit, Wolfson Medical Center, Holon, Israel

P2_98 HOMOZYGOUS DUPLICATION OF PMP22: A CASE REPORT

Janel Phetteplace

Phetteplace JE, Saade D, Bacon C, Shy ME. University of Iowa Hospitals and Clinics, Iowa City, IA, USA

P2_99 THE GERMAN CHARCOT-MARIE-TOOTH DISEASE NETWORK (CMT-NET): DISEASE SEVERITY AND PROGNOSTIC BIOMARKERS FROM BLOOD AND SKIN OF CMT1A PATIENTS

Thomas Prukop

(1,2,3) T Prukop, (4) N Garcia-Angarita, (4) LS König, (5) D Pieper, (5) B Dräger, (4) S Thiele, (5) D Hüttemann, (4) B Schlotter-Weigel, (4) MC Walter, (5) P Young and (1,3) MW Sereda. (1) University Medical Center Göttingen, Department of Clinical Neurophysiology, Göttingen, Germany; (2) University Medical Center Göttingen, Institute of Clinical Pharmacology, Göttingen, Germany; (3) Max-Planck-Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany; (4) Friedrich-Baur-Institute, Department of Neurology, Ludwig- Maximilians-Universität, Munich, Germany; (5) Department of Sleep Medicine and Neuromuscular Disorders, University of Münster, Münster, Germany

P2_100 DEVELOPMENT OF BEST PRACTICE GUIDELINES FOR PAEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

Joshua Burns

(1,2,3) Yiu EM, (2,4,5) Burns J, (4,5) Menezes MP, and (1,2,3) Ryan MM for the Paediatric CMT Best Practice Guidelines Consortium. (1) Royal Children's Hospital Melbourne, Melbourne, Victoria, Australia; (2) Murdoch Childrens Research Institute, Melbourne, Victoria, Australia; (3) University of Melbourne, Melbourne, Victoria, Australia; (4) University of Sydney, New South Wales, Australia; (5) Sydney Children's Hospitals Network (Randwick and Westmead), New South Wales, Australia

P2_101 CHARCOT-MARIE-TOOTH NEUROPATHY MISDIAGNOSED AS CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: A CASE SERIES

Marta Ruiz
Ruiz M1 Campagnolo M1, Salvalaggio A1, Cacciavillani M2, Taioli F3, Fabrizi GM3, Briani C1. 1Department of Neuroscience, Neurology Unit, University of Padova, Padova, Italy 2 Data Medica Group, EMG Unit, CEMES, Padova, Italy 3 Department of Neurological and Movement Sciences, University of Verona, Verona, Italy

P2_102 NERVE ULTRASOUND, MRI NEUROGRAPHY AND DIFFUSION TENSOR IMAGING ANALYSIS REVEALED PECULIAR NERVE ABNORMALITIES IN FRIEDREICH'S ATAXIA

Alessandro Salvalaggio
(1) Salvalaggio A, (2) Coraci D, (3) Cacciavillani M, (1) Ruiz M, (4) Manganelli F, (4) Antenora A, (4) Filla A, (4) Santoro L, (5) Gasparotti R, (6) Padua L, (1) Briani C. (1) Department. of Neurosciences, University of Padova, Padova; (2) Board of Physical Medicine and Rehabilitation, Department of Orthopaedic Science, "Sapienza" University, Rome, Italy; (3) CEMES-EMG Lab, Data Medica Group, Padova; (4) Department of Neurosciences, Reproductive Sciences and Odontostomatology, University Federico II of Naples, Naples, Italy; (5) Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia; (6) Department of Geriatrics, Neurosciences and Orthopaedics, Università Cattolica del Sacro Cuore, Rome, Italy

P2_103 THE AIFM1 p.F210S MUTATION CAUSES AN APOPTOTIC FAILURE AND ACTIVATION OF SENESCENT PROGRAM IN FIBROBLASTS DERIVED FROM PATIENT BIOPSIES

Paula Sancho
(1,2) Sancho P, (1,2) Sánchez-Monteagudo A, (1,2) Collado-Padilla A, (3,4) Marco C, (5) Domínguez C, (6) Camacho A, (2,4,7) Knecht E, (1,2,8) Espinós E*, (1,2,8) Lupo V. (1) Unit of Genetics and Genomics of Neuromuscular and Neurodegenerative Disorders, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; (2) INCLIVA & IIS La Fe Rare Diseases Joint Units, Valencia, Spain; (3) Unit of Structural Enzymopathology, Instituto de Biomedicina de Valencia, (4) CIBER of Rare Diseases (CIBERER), Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; (5) Department of Neurology, Hospital 12 de Octubre, Madrid, Spain; (6) Department of Neuropediatrics, Hospital 12 de Octubre, Madrid, Spain; (7) Unit of Intracellular Protein Degradation, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain; (8) Department of Genomics and Traslational Genetics, Centro de Investigación Príncipe Felipe (CIPF), Valencia, Spain

P2_104 SARM1 AND NAD INVOLMENT IN AXONAL DEGENERATION IN DEMYELINATING HEREDITARY NEUROPATHY CMT1A

Jens Schmidt
Schmidt J, Gess B. Uniklinikum RWTH Aachen, Germany

P2_105 IDENTIFICATION OF FIVE NOVEL MUTATIONS IN BRAZILIAN FAMILIES WITH X-LINKED CMT

Pedro José Tomaselli
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TUESDAY 11 JULY 2017

7.30 - 8.30 **Clinical Trial Updates** AUDITORIUM

Poster Session 3 Viewing TRAMUNTANA FOYER
(see end of Tuesday 11 July 2017 for poster titles)

Coffee TRAMUNTANA HALL

Plenary Lecture and Platform Session 4

Chairs: **David Bennett** and **Amy Rumora**

8.30 - 9.00 **Plenary 4: PJ Dyck Lecture** AUDITORIUM
MECHANOTRANSDUCTION AND PAIN
Gary Lewin

9.00 - 10.00 **Platform Session 4** AUDITORIUM

9.00 **O5_1**
TRPV4-MEDIATED DISRUPTION OF CALCIUM SIGNALING AND MITOCHONDRIAL AXONAL TRANSPORT IN A DROSOPHILA MODEL OF CMT2C
Brian Woolums
Woolums BM, Tabuchi M, Sung H, Sullivan JM, Mamah C, Yang M, Blum ID, Wu MN, Sumner CJ, Lloyd TE. 1Johns Hopkins University, Baltimore, USA

9.15 **O5_2**
IMPLICATION OF RARE Nav1.7 VARIANTS IN PAINFUL DIABETIC NEUROPATHY
Andreas Themistocleous
(1) Themistocleous AC, (1) Blesneac I, (2) Fratter C, (3) Cox JJ, (4) Tesfaye S, (4)Shillo PR, (1) Ramirez JD, (5) Rice ASC, (1) Bennett DLH (1) Nuffield Department of Clinical Neurosciences, University of Oxford, UK; (2) Oxford Medical Genetics Laboratories, Oxford University Hospitals NHS Foundation Trust, The Churchill Hospital, Oxford, UK; (3) Molecular Nociception Group, University College London, London, UK; (4) Diabetes Research Unit, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, U.K; (5) Pain Research Group & Pain Medicine, Imperial College London, Chelsea and Westminster Hospital Campus, London, UK

9.30 **O5_3**
RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA RESULTS IN PAINFUL SMALL FIBRE NEUROPATHY
Margarita Calvo
(1) Calvo M, (2) Bennett DLH (1) Pontificia Universidad Catolica de Chile, Santiago, Chile; (2) NDCN Oxford University, UK

9.45 **O5_4**
A RANDOMIZED CONTROLLED TRIAL OF THE EFFICACY, SAFETY, AND TOLERABILITY OF LACOSAMIDE IN PATIENTS WITH GAIN-OF-FUNCTION NAv1.7 MUTATIONS-RELATED SMALL FIBER NEUROPATHY, THE LENSS STUDY
Bianca de Greef
(1) de Greef BTA, (1) Geerts M, (1, 2) Faber CG1, Merkies ISJ, (1) Hoeijmakers JGJ. (1) Department of Neurology, School of Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands. (2) Department of Neurology, St. Elisabeth Hospital, Willemstad, Curaçao.

10.00 - 10.30 Coffee TRAMUNTANA HALL

10.30 - 12.00 Oral Poster Presentations Session 4 AUDITORIUM

Chairs: **Wendy Campana** and **Margarita Calvo**

OP4_1 REVERSAL OF PAINFUL DIABETIC NEUROPATHY BY CONTROL OF NOCICEPTOR EXCITABILITY

Daniela Maria Menichella

(1) Bhattacharyya BJ, (1) Jayaraj, ND, (2) Belmadani A, (2) Ren D, (1) Rathwell, CA, (1) Hackelberg S, (2) Miller RJ and (1) Menichella, DM. (1) Department of Neurology Northwestern University, Chicago, IL, USA, (2) Department of Pharmacology, Northwestern, Chicago, IL, USA

OP4_2 SENSORY PHENOTYPE AND RISK FACTORS FOR PAINFUL DIABETIC NEUROPATHY: A CROSS SECTIONAL OBSERVATIONAL STUDY

Josef Bednarik

(1,2) Vlckova E, (1,2) Raputova J, (1,2) Srotova I, (3) Sommer C, (3) Üçeyler N, (4) Birklein F, (4) Rebhorn C, (5) Rittner HL, (1,2) Kovalova E, (1,2) Nekvapilova E, (6) Belobradkova J, (7) Olsovsky J, (8) Weber P, (9) Dusek L, (9) Jarkovsky J, (1,2) Bednarik J. (1) Central European Institute of Technology, Masaryk University, Brno, Czech Republic (2) Department of Neurology, University Hospital Brno, Brno, Czech Republic (3) Department of Neurology, University of Würzburg, Germany (4) Department of Neurology, University Medical Center, Mainz, Germany (5) Department of Anesthesiology, Centre for interdisciplinary Pain Medicine, University Hospital Würzburg, Germany (6) Diabetologic Centre, Department of Internal Medicine and Gastroenterology, University Hospital Brno (7) Diabetologic Centre, St. Anne University Hospital, Brno, Czech Republic (8) Department of Internal Medicine, Geriatrics and Practical Medicine, University Hospital Brno, Brno, Czech Republic (9) Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic

OP4_3 PHYSIOLOGICAL CHARACTERIZATION OF NOCICEPTORS INNERVATING THE PLANTAR SKIN FOLLOWING NEUROPATHIC INJURY

Johannes Kühnemund

1) Kühnemund J, (2) Wetzel C, (2) Bégay V, (3) Moshourab R and (2) Lewin GR. (1) MDC & BIH, Berlin, Germany; (2) MDC, Berlin, Germany; (3) Charité, Berlin, Germany

OP4_4 CHRONIC NON-FREEZING COLD INJURY RESULTS IN NEUROPATHIC PAIN DUE TO A SENSORY NEUROPATHY

Tom Vale

(1) Vale TA, (1) Symmonds M, (2) Polydefkis M, (3) Rice A, (1) Themistocleous AC, (1) Bennett DLH. (1) Nuffield Department of Clinical Neurosciences, University of Oxford, United Kingdom; (2) Department of Neurology, Johns Hopkins University School of Medicine, USA; (3) Pain Research Group, Imperial College London, UK

OP4_5 EVALUATION OF MOLECULAR INVERSION PROBE VERSUS TruSeq® CUSTOM-NEXT GENERATION SEQUENCING METHODS TO IDENTIFY GENETIC VARIATIONS IN PAINFUL NEUROPATHIES- THE PROPANE STUDY

Rowida Almomani

(1) Almomani R, (2) Marchi M, (1) Lindsey P, (3) Sopacua M, (4) Santoro S, (1) Smeets H, (2) Lauria G, (4) Boneschi FM, (5 6 7) Dib-Hajj S, (5 6 7) Waxman SG, (3 8) Merkies ISJ, (3) Faber CG, (1) Gerrits MM; PROPANE Study Group (1) Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, the Netherlands; (2) Neuroalgology Unit, IRCCS Foundation, "Carlo Besta", Milan, Italy; (3) Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands; (4) Laboratory of Genetics of Neurological Complex Disorders, Institute of Experimental Neurology (INSPE), Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy; (5) Department of Neurology and (6) Center for Neuroscience and Regeneration Research, Yale University School of Medicine, New Haven, and (7) Center for Neuroscience and Regeneration Research, Veterans Affairs Medical Center, West Haven, USA; (8) Department of Neurology, St Elisabeth Hospital, Willemstad, Curaçao

OP4_6 TRPV1 EXPRESSION IN HUMAN PERIPHERAL SENSORY NERVES AND RELATIONSHIP TO NEUROPEPTIDES CGRP AND SP

Baohan Pan

(1) Pan B, (2) Karlsson P, (1) Liu Y, (3) Caterina M, (1) Polydefkis M. (1) Department of Neurology, Johns Hopkins University, Baltimore, USA; (2) Danish Pain Research Center and Department of Clinical Medicine, Aarhus University Hospital, Denmark; (3) Department of Neurosurgery, Johns Hopkins University, Baltimore, USA

OP4_7 SMALL FIBER NEUROPATHY CHARACTERIZATION IN THE SOD1G93A ALS MOUSE MODEL

Miguel Angel Rubio

(1,2) Rubio MA, (2) Herrando-Grabulosa M, (2) Vilches JJ, (2) Navarro X. (1) Neuromuscular Unit, Department of Neurology, Hospital del Mar. Barcelona, Spain; (2) Department of Cell Biology, Physiology and Immunology, Institute of Neurosciences and CIBERNED, Universitat Autònoma de Barcelona, Bellaterra, Spain

OP4_8 AN IN VIVO AND IN VITRO NEUROPHYSIOLOGICAL APPROACH TO ACUTE AND CHRONIC OXALIPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

Paola Alberti

(1) Alberti P, (2) Lecchi M, (1,2,3) Monza L, (2) Pastori V, (1) Fumgalli F, (1) Pozzi E, (2) Becchetti A, (4) Bostock H, (1) Cavaletti G. (1) School of Medicine and Surgery- PhD Program in Neuroscience - University of Milano-Bicocca, Monza, Italy; (2) Department of Biotechnology and Bioscience - University of Milano-Bicocca, Milan, Italy; (3) PhD program in Translational and Molecular Medicine (DIMET) - University of Milano-Bicocca, Milan, Italy; (4) University College London, London, U.K

OP4_9 PROLONGED POST TETANIC POTENTIATION

Ludwig Gutmann

Gutmann L, Shy M. University of Iowa, Iowa City, USA

OP4_10 THE GENERATOR SITE IN ACQUIRED AUTOIMMUNE NEUROMYOTONIA

Miguel Oliveira Santos

(1,2) Oliveira Santos M, (1,3) Swash M, (1,2) de Carvalho M. (1) Institute of Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Portugal; (2) Department of Neurology, Department of Neurosciences and Mental Heath, Hospital de Santa Maria, Centro Hospitalar Lisboa Norte, Lisbon, Portugal; (3) Departments of Neurology and Neuroscience, Barts and the London School of Medicine, Queen Mary University of London, United Kingdom

OP4_12 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL EVALUATING THE SAFETY AND EFFICACY OF L- SERINE IN SUBJECTS WITH HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE 1 (HSAN1)

Vera Fridman

(1) Fridman, V, (2) Novak P, (1) David W, (1) Macklin EA, (1) McKenna-Yasek, D, Walsh K, (1) Oaklander AL, (2) Brown R, (3) Hornemann T, (1) Eichler F. (1) Massachusetts General Hospital, Boston, MA, USA, (2) University of Massachusetts Medical School, Worcester, USA, (3) University Hospital Zurich, Zurich, Switzerland

OP4_13 HUMAN IPSC DERIVED SENSORY NEURON MODEL OF HEREDITARY SENSORY NEUROPATHY TYPE 1 (HSN1)

Umaiyal Kugathasan

(1) Kugathasan U, (2) Clark AJ, (3) Suriyanarayanan S, (1) Laurá M, (1,4) Wilson E, (4) Kalmar B, (1,4) Greensmith L, (3) Hornemann T, (1) Reilly MM* and (2) Bennett DLH*. 1MRC Centre for Neuromuscular Diseases, London, UK; 2Neural Injury Group, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK: 3Institute for Clinical Chemistry, University Hospital Zurich, Switzerland; 4Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London, UK

OP4_15 NEUROPHYSIOLOGICAL FINDINGS IN ASYMPTOMATIC STAGE OF FAMILIAL AMYLOID NEUROPATHY: A CASE CONTROL STUDY

Guillemette Beaudonnet

(1) Beaudonnet G, (1) Prud'hon S, (2) Cauquil C, (2) Labeyrie C, (2) Not A, (1) Bouilleret V, (2) Adams D. (1) Neurophysiology CHU Bicêtre, Le Kremlin Bicêtre, France, (2) Neurology CHU Bicêtre, Le Kremlin Bicêtre, France

12.00 - 14.00 **Poster Viewing** **TRAMUNTANA FOYER**

12.00 - 14.00 Lunch

12.00 - 13.00 Sponsor Symposium 3: CSL Behring AUDITORIUM

INDIVIDUALIZED THERAPY IN CIDP
Chair: **Jeffrey A Allen**, Minneaoplis, MN, USA

Interlaken Leadership Award: Announcement of the 2017 winners
Gabriela Espinoza, CSL Behring, King of Prussia, PA, United States

Wear-off with IVIG and what it means in clinical practice
Robert Hadden, King's College Hospital, London, United Kingdom

IgG metabolism and its impact on individualized therapy
Krista Kuitwaard, Erasmus MC, Rotterdam, The Netherlands

Immunology of CIDP. Will knowledge of antibodies change treatment?
Luis Querol, Hospital Sant Pau, Barcelona - Spain

Questions and answers

12.00 - 13.00 Sponsor Symposium 3: Terumo BCT TRAMUNTANA 1+2 ROOM

PLASMA EXCHANGE FOR PNS & NEUROMUSCULAR DISEASES: NOVEL ADVANCES IN PRACTICE

Using a panel discussion and interactive format with audience participation, this symposium will explore the use of therapeutic plasma exchange for peripheral neuropathies and neuromuscular diseases: indications, mechanisms of action including effects on the immune system, appropriate treatment and expectations, short and long term use, and safety including vascular access

Anupam Bhattacharjee BSC PHD MBBS MRCP(UK) MRCP(UK)(NEUROLOGY) – Consultant Neurologist, Royal Free Hospital (London) & Lister Hospital (Stevenage)

Hans Katzberg MD, FRCPC, MSc - Associate Professor of Neurology, University of Toronto, Toronto General Hospital (University Health Network (UHN))

Benit Maru BSc, MSc, MBChB, PhD – Global Medical Affairs, Terumo BCT

Plenary Lecture and Platform Session 5

Chairs: **Xavier Navarro** and **Jorge Galino**

14.00 - 14.30 Plenary 5: - PK Thomas Lecture AUDITORIUM

THE CONTROL OF WALLERIAN DEGENERATION AND ITS RELEVANCE TO PERIPHERAL NEUROPATHY

Michael Coleman

14.30 - 15.30 Platform Session 5 AUDITORIUM

14.30 **O6_1**

ATP1A1 REPRESENTS A SIGNIFICANT NOVEL DOMINANT CMT2 GENE

Stephan Zuchner

(1) Lassuthova, P, (2) Rebelo, A, (3) Ravenscroft, G, (3) Lamont, P, (3) Baxter, M, (3) Ong, R, (8) Davis, M, (7) Manganelli, F, (2) Tao, F, (2) Saghira, C, (2) Abreu, L, (6) Bai, Y, (4) Isom, D, (3) Laing, N, (5) Choi, B-O, (1) Seeman, P, (6) Shy, M, (7) Santoro, L, (2) Zuchner S. (1) DNA Laboratory, Department of Paediatric Neurology, 2nd Faculty of Medicine, Charles University in Prague and University Hospital Motol, Prague, Czech Republic; (2) Dr. John T. Macdonald Foundation Department of Human Genetics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, USA; (3) Centre for Medical Research, University of Western Australia and Harry Perkins Institute of Medical Research, Nedlands, Australia; (4) Department of Pharmacology, Sylvester Comprehensive Cancer Center, and Center for Computational Sciences, University of Miami, Miami, USA; (5) Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; (6) Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, USA (7) Department of Neuroscience, Reproductive Sciences and Odontostomathology, Naples, Italy

14.45 **O6_2**

PLASMA NEUROFILAMENT LIGHT CHAIN LEVELS ARE RAISED IN PATIENTS WITH INHERITED PERIPHERAL NEUROPATHY AND CORRELATE WITH DISEASE SEVERITY

Alexander Rossor

(1) Rossor AM, (2) Sandelius A, (3) Adiutori R, (3) Malaspina A, (2) Blennow K, (2,4) Zetterberg H, (1) Reilly MM. (1) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology and National Hospital for Neurology and Neurosurgery, London, UK; (2) Department of Psychiatry and Neurochemistry, Sahlgrenska Academy at the University of Gorthenburg, Sweden; (3) Trauma and Neuroscience Centre, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK; (4) Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK

15.00 **O6_3**

SARM1 DELETION AND WLDS ARE NEUROPROTECTIVE IN THREE MODELS OF CHEMOTHERAPY INDUCED PEIRPHERAL NEUROPATHY

Ahmet Hoke

Fisgun A, Luan X and Hoke A. Johns Hopkins University, Baltimore, USA

15.00 **O6_4**

MUTATIONAL BURDEN ANALYSIS IN INHERITED PERIPHERAL NEUROPATHIES

Dana Bis

(1) Bis D, (1) Tao F, (1) Abreu, L, (2) Sleiman P, (2) Hakonarson H, Inherited Neuropathy Consortium, (1) Zuchner S. (1) Dr. J.T. MacDonald Department for Human Genetics, Hussman Institute for Human Genomics, University of Miami, Miami, Florida, USA. (2) Center for Applied Genomics, the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

15.30 - 17.00 Oral Poster Presentations Session 5 AUDITORIUM

OP5_1 PERIPHERAL NEUROPATHY RESEARCH REGISTRY (PNRR)

Simone Thomas

(1) Thomas S, (2) Ajroud-Driss S, (3) Dimachkie M, (4) Freeman R, (5) Simpson D, (6) Smith G and (1) Hoke A(1) Johns Hopkins School of Medicine, Baltimore, USA; (2) Northwestern University Medical Center, Chicago, USA; (3) Kansas University Medical Center, Kansas City, USA (4); Beth Israel Deaconess Medical Center, Boston, USA; (5) Icahn School of Medicine at Mount Sinai Medical Center, New York, USA; (6) University of Utah Medical Center, Salt Lake City, Utah, USA.

OP5_2 POLYNEUROPATHY RELATES TO IMPAIRMENT IN DAILY ACTIVITIES, WORSE GAIT AND FALL-RELATED INJURIES

Rens Hanewinckel

1, 2) Hanewinckel R, (2, 3) Drenthen J, (1) Verlinden VJA, (1) Darweesh SKL, (3) van der Geest JN, (1, 5) Hofman A, (2) van Doorn PA, (1) Ikram MA. (1) Department of Epidemiology; (2) Department of Neurology; (3) Department of Neuroscience; (4) Department of Clinical Neurophysiology, Erasmus University Medical Center, Rotterdam, the Netherlands; (5) Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States

OP5_3 IENF AND MC ARE EARLY MARKERS OF PERIPHERAL INVOLVEMENT IN PD AND ARE DIFFERENTLY AFFECTED BY LDOPA TREATMENT

Maria Nolano

(1) Nolano M, (1) Provitera V, (1) Stancanelli A, (1) Caporaso G, (1) Saltalamacchia AM, (1) Borreca I, (1) Lullo F, (1) Califano F, (1)Lanzillo B, (2)Iodice R, (2)Manganelli F, (3)Barone P, (2)Santoro L. (1) IRCCS "Salvatore Maugeri" Foundation, Institute,of Telese Terme (BN), Italy; (2) "Maugeri" Clinical and Scientific Institutes IRCCS, Institute of Telese Terme (BN), Italy; (3) Center for Neurodegenerative Diseases (CEMAND), Department of Medicine and Surgery, Neuroscience Section, University of Salerno, Italy

OP5_4 A RANDOMIZED TRIAL OF AN AUTOMATED CIPN SYMPTOM MANAGEMENT SYSTEM

Noah Kolb

(1) Kolb N, (2) Smith AG, (2) Singleton JR, (2) Beck S, (1) Howard D, (1) Dittus K, (2) Karafiath S, (2) Mooney K. (1) University of Vermont, Burlington, VT, USA, (2) University of Utah Health, SLC, UT, USA

OP5_5 ROLE OF THE ALPHA SECRETASE TACE DURING WALLERIAN DEGENERATION

Marta Pellegatta

(1) Pellegatta M, (1) Canevazzi P, (1) Forese MG, (2) Podini P, (2) Quattrini A and (1) Taveggia C. (1) Division of Neuroscience and INSPE, Axo-Glia Interaction Unit, San Raffaele Scientific Institute, Milan, Italy; (2) Division of Neuroscience and INSPE, Experimental Neuropathology Unit, San Raffaele Scientific Institute, Milan, Italy

OP5_6 SELECTIVE MUSCARINIC RECEPTOR ANTAGONISM ACTIVATES THE ERK/MAPK PATHWAY IN ADULT SENSORY NEURONS

Mohammad Golam Sabbir

(1) Sabbir MG, (2) Fernyhough P. (1) Division of Neurodegenerative Disorders, St. Boniface Hospital Albrechtsen Research Centre, Winnipeg, MB, Canada; (2) Department of Pharmacology & Therapeutics, University of Manitoba, MB, Canada

OP5_7 CARPAL TUNNEL SYNDROME AS A HUMAN IN VIVO MODEL TO STUDY LARGE FIBER REGENERATION

Vincenzo Provitera

(1) Provitera V, (1) Caporaso G, (1) Stancanelli A, (1) Piscosquito G, (1) Di Caprio G, (1) Saltalamacchia AM, (2) Santoro L, (1) Nolano M. (1) "Maugeri" Clinical and Scientific Institutes IRCCS, Institute of Telese Terme (BN), Italy; (2) Department of Neurosciences, Reproductive and Odontostomatological Sciences, University 'Federico II' of Naples, Naples, Italy

OP5_8 CMAP SCAN ANALYSIS IN MULTIFOCAL MOTOR NEUROPATHY

Boudewijn Sleutjes

Sleutjes BTHM, Kovalchuk M, van Schelven LJ, van den Berg L, Franssen, H. Department of Neuromuscular Disorders, University Medical Center Utrecht, Utrecht, The Netherlands

OP5_9 CUTANEOUS NERVE FIBER ANALYSIS AS A BIOMARKER IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

Gigi Ebenezer

(1) Ebenezer GJ, (1) Liu Y, (2) Judge DP, (1) Cunningham K, (3) Truelove S, (1) Carter ND, (1) Sebastian B, (1) Byrnes K, (1) Polydefkis M. (1) Department of Neurology, Johns Hopkins University, Baltimore, MD, USA; (2) Division of Cardiology, Johns Hopkins University, Baltimore, MD, USA; (3) Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

OP5_10 A KNOCK-IN / KNOCK-OUT MOUSE MODEL FOR SMALL HEAT SHOCK PROTEIN HSPB8 MIMICKING DISTAL HEREDITARY MOTOR NEUROPATHY AND MYOFIBRILLAR MYOPATHY

Vincent Timmerman

(1) Bouhy D, (2) Katona I, (1) Juneja M, (1) Haidar M, (1) Holmgren A, (1) De Winter V, (1) Irobi J, (2) Weis J, (1) Timmerman V. (1) Peripheral Neuropathy Research Group, Institute Born Bunge, University of Antwerp, Antwerp, Belgium; (2) Institute of Neuropathology, University Hospital, RWTH Aachen University, Aachen, Germany

OP5_11 PATHOGENESIS OF CHARCOT-MARIE-TOOTH DISEASE TYPE 2C DUE TO MUTATIONS IN TRPV4
Brett McCray
McCray B, Sullivan J, Woolums B, Aisenberg W, Lloyd T, Sumner C. Johns Hopkins University, Baltimore, USA

OP5_12 NOVEL PHE210LEO MISSENSE MUTATION IN AIFM1 GENE IS ASSOCIATED WITH AN AXONAL POLYNEUROPATHY
Ryan Castoro
Castoro R, Wang M, Simmons M, Hu B, Li J. Department of Neurology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

OP5_13 NOVEL NEFH MUTATIONS AS A CAUSE OF AN AUTOSOMAL AXONAL FORM OF CHARCOT-MARIE-TOOTH DISEASE WITH PROXIMAL MUSCLE INVOLVEMENT
Cécile Delorme
(1) Delorme C, (2,3) Jacquier A, (4) Morales-Juntas R, (5) Zuchner S., (6) Sole G, (2,7) Schaeffer L, (8) Stojkovic T, (3) Latour P. (1) Département de Neurologie, Hôpital Pitié-Salpêtrière, Paris, France; (2)Institut NeuroMyoGène, Université Lyon1 - CNRS UMR 5310 - INSERM U1217, Lyon, France; (3)Unité fonctionnelle de neurogénétique moléculaire, CHU de Lyon - HCL groupement Est, Bron, France; (4)Clinique du motoneurone et pathologies neuromusculaires, CHRU de Montpellier, Montpellier, France; (5)Dr John T. MacDonald Foundation Department of Human Genetics, Institute of Human Genomics, University of Miami, Miller School of Medicine, Miami, USA; (6) Centre de références des maladies neuromusculaires, CHU de Bordeaux, Bordeaux, France; (7)Centre de Biotechnologie Cellulaire, CBC Biotec, CHU de Lyon - HCL groupement Est, Faculté de médecine Lyon Est, Bron, France; (8)Institut de Myologie, Hôpital Pitié-Salpêtrière, Paris, France

OP5_14 ALTERED NEUROFILAMENT DISTRIBUTION IN HUMAN CMT2E MOTOR NEURON AXONS
Mario Saporta
(1,2) de Moraes Maciel R, (1) Cutrupi AN, (2) Rebelo A, (2) Zuchner S, (1,2) Saporta MA (1) Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA; (2) Department of Human Genetics, Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA

OP5_15 MODELLING BROWN-VIALETTO-VAN LAERE SYNDROME IN C. ELEGANS
Megan Brewer
(1,2) Brewer MH, (2) Attrill G, (1) Ellis M, (1) Ly C, (1,2,3) Nicholson GA, (4,5) Menezes MP*, (1,2,3) Kennerson ML*. (1) Northcott Neuroscience Laboratory, ANZAC Research Institute, Sydney, Australia; (2) Sydney Medical School, University of Sydney, Sydney, Australia; (3) Molecular Medicine, Concord Repatriation General Hospital, Sydney Australia; (4) The Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Sydney, Australia; (5) Pediatrics and Child Health, University of Sydney, Sydney, Australia; *Equal last author

17.00 - 18.00 **Poster Viewing** TRAMUNTANA FOYER

17.00 - 18.00 Coffee TRAMUNTANA HALL

Plenary Lecture and Awards

18.00 - 19.00 **Presidential Talk - Prizes** AUDITORIUM
Introduced by
Mike E. Shy

HUMANS - THE ULTIMATE ANIMAL MODEL
Mary M. Reilly

19.00 - 22.00 **PNS Closing Dinner** TRAMUNTANA

19.00 - 20.00 Put up posters for Poster Session 4 &
Oral Poster Presentations Session 6 TRAMUNTANA FOYER

Poster Session 3 TRAMUNTANA FOYER

P3_1 SUBACUTE COMBINED DEGENERATION CAUSED BY CHRONIC ATROPHIC GASTRITIS WITH SPURIOUS ELEVATION OF VITAMIN B12 LEVEL

Min Su Park

Park JG, Park MS. Yeungnam University College of Medicine, Daegu, Korea

P3_2 SEQUENTIAL EDX TESTING IDENTIFIES DIFFERENTIAL SUSCEPTIBILITY OF THE MEDIAN NERVE TO PROLONGED WRIST EXTENSION IN NORMAL SUBJECTS

Yann Pereon

(1) Péréon Y, (1) Nguyen A-L, (1) Leclair-Visonneau L, (1) Fayet G, (2) Nguyen J-M, (1) Magot A. (1) Laboratoire d'Explorations Fonctionnelles, Hôtel-Dieu, Nantes, France ; (2) Département de Statistiques Médicales, Hôtel-Dieu, Nantes, France

P3_3 ARSENIC TRIOXIDE INDUCED PERIPHERAL NEUROPATHY: PROSPECTIVE EVALUATION OF TWO PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

Marta Ruiz

(1) Ruiz M, (2) Lessi F, (3) Cacciavillani M, (2) Riva M, (1) Salvalaggio A, (1) Campagnolo M, (1) Briani C. (1) Neurology,Department of Neuroscience, University of Padova; (2) Hematology and Clinical Immunology Unit, Department of Medicine, University of Padova; (3) CEMES, Data Medica Group, Padova, Italy

P3_5 IMPAIRMENT OF MITOCHONDRIAL TRAFFICKING IN DORSAL ROOT GANGLION NEURONS IS DEPENDENT ON HYDROCARBON CHAIN LENGTH OF SATURATED FATTY ACIDS

Maegan Tabbey

(1) Rumora AE, (1) Tabbey MA, (1) LoGrasso G, (1) Dolkowski J, (1) Haidar J, (2) Lentz SI, and (1) Feldman EL. (1) Department of Neurology, University of Michigan, Ann Arbor, USA; (2) Department of Internal Medicine, Division on Metabolism, Endocrinology and Diabetes, University of Michigan, Ann Arbor, USA

P3_6 THE ASSOCIATION BEWTEEN THE METABOLIC SYNDROME AND NEUROLOGIC OUTCOMES IN A BARIATRIC SURGERY POPULATION

Emily Villegas-Umana

(1) Callaghan BC, (2) Villegas-Umana E, (3) Reynolds E, (4) Averill S, (5) Feldman EL. (1) University of Michigan, Ann Arbor, USA

P3_7 INCIDENCE OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY AND LONG TERM DISEASE BURDEN ON CANCER SURVIVORS IN A POPULATION-BASED COHORT

Nathan Staff

Shah A, Hoffman EM, Klein CJ, Staff NP. Mayo Clinic, Rochester, USA

P3_8 TREATMENT INDUCED NEUROPATHY OF DIABETES IN PATIENTS WHO HAVE UNDERGONE BARIATRIC SURGERY

Joel Wong

(1) Wong SHJ, (2) Koh SJ, (1) Lee BJH, (3) Chng YSK, (3) Pawa C, (4) Subramaniam T, (4) Cheng KSA, (2) T. Umapathi. (1) Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore; (2) National Neuroscience Institute, Singapore; (3) Yong Loo Lin School of Medicine, National University Singapore, Singapore; (4) Khoo Teck Puat Hospital, Singapore

P3_9 PREVALENCE OF PERIPHERAL NEUROPATHY AMONG FREQUENT FLYERS – IS THERE A LINK TO "AEROTOXIC SYNDROME"?

Maryam Balke

(1) Balke M, (1) Sprenger A, (1) Wunderlich G, (3) Stettner M, (1,2) Fink GR, (1) Lehmann HC. (1) University Hospital of Cologne, Germany; (2) INM-3 Research Centre Jülich, Jülich, Germany; (3) University Hospital of Essen, Germany

P3_10 ESTABLISHMENT OF THE COCULTURE SYSTEM OF IMMORTALIZED SCHWANN CELLS IFRS1 AND MOTOR NEURON-LIKE CELLS NSC-34

Kazunori Sango

Sango K, Takaku S, Niimi N, Yako H. Diabetic Neuropathy Project, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan

P3_11 THE EFFECT OF CURCUMIN ON PERIPHERAL NERVE REGENERATION

Özgür Demir
(1) Kılınç M, (1) Oksuz E, (1) Demir O, (1) Ersay FD, (2) Cevik B. (1) Gaziosmanpaşa University, Deparment of Neurosurgery, Tokat, Turkey; (2) Gaziosmanpaşa University, Deparment of Neurology, Tokat, Turkey

P3_12 TIME-COURSE CHARACTERIZATION OF FOREIGN BODY REACTION TO IMPLANTED DEVICES IN RAT PERIPHERAL NERVE

Natalia de la Oliva
De la Oliva N, Del Valle J, Navarro X. Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain

P3_14 IMPLICATIONS OF SKIN BIOPSY TISSUE THICKNESS ON STUDY OUTCOMES

Christopher Gibbons
Gibbons C, Wang N, McCormick M, Freeman R. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, USA

P3_15 RECURRENT PERIPHERAL AND CENTRAL DEMYELINATION IN A SERONEGATIVE PATIENT

Can Ebru Bekircan-Kurt
(1, 2) Bekircan-Kurt CE, (1) Yildiz G, (1) Temuçin Ç, (1) Kurne AT, (1, 2) Tan E, (1, 2) Erdem-Ozdamar SE Hacettepe University (1) Department of Neurology, (2) Neuromuscular Disease Research Laboratory Ankara, Turkey

P3_16 OPTIMIZING ELECTRODIAGNOSTICS FOR GUILLAIN-BARRE SYNDROME: CLUES FROM CLINICAL PRACTICE

Hiew Fu Liong
(1) Fu Liong H, (2) Yusuf R. (1) Regional Neuromuscular Clinic, Queen Elizabeth Hospital, University Hospitals of Birmingham, Birmingham, United Kingdom; (2) School of Life and Health Sciences, Aston Brain Centre, Aston University, Birmingham, United Kingdom

P3_17 INFLUENCE OF IVIG ON NERVE EXCITABILITY IN MULTIFOCAL MOTOR NEUROPATHY

Maria Kovalchuk
1) Kovalchuk M, (1) Franssen H, (2) van Schelven LJ, (1) van den Berg L, (1) Sleutjes BTHM. (1) Department of Neuromuscular Disorders, University Medical Centre Utrecht, Utrecht, The Netherlands; (2) Department of Medical Technology and Clinical Physics, University Medical Centre Utrecht, Utrecht, The Netherlands

P3_18 HEMOLYTIC SIDE EFFECTS OF IVIG: MODELING PREDICTS RISK REDUCTION WITH ANTI-A/B IMMUNOAFFINITY CHROMATOGRAPHY AND TO A LESSER EXTEND WITH ANTI-A DONOR SCREENING

Alphonse Hubsch
(1) Mallik R, (2) Hubsch A, (2) Gaida A, (3) Barnes D. (1) CSL Behring, KOP, US; (2) CSL Behring, Bern, Switzerland, (3) CSL Behring, Ottawa, Canada

P3_19 THE VALUE OF ELECTROPHYSIOLOGICAL TYPING AND CONDUCTION BLOCK FOR PREDICTION OF FUNCTIONAL OUTCOME IN GUILLAIN-BARRE SYNDROME

Minsheng Liu
Niu JW, Cui LY, Guan YZ, Liu MS. The Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

P3_20 CLINICAL AND ELECTRODIAGNOSTIC FEATURES OF GANGLIONOPATHIES WITH SPECIAL REFERENCE TO ULNAR SENSORY-MOTOR AMPLITUDE RATIO(USMAR) FROM A TERTIARY CARE CENTER IN INDIA

Anjan Pyal
Pyal A, Sireesha Y, Neeharika ML, Meena AK. Department of Neurology Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India

P3_21 DOES ELECTROPHYSIOLOGY AND TREATMENT RESPONSE DIFFER IN IDIOPATHIC VS DIABETIC CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)?

Anza Memon
Memon A, Madani S, Ahmad BK, Schultz L, Grover, Arcila-londono X, Sripathi N. Department of Neurology, Henry Ford Hospital, Detroit, Michigan, USA

P3_22 ASSESSMENT OF INDIVIDUAL RESPONSE TO INTRAVENOUS IMMUNOGLOBULIN USING DAILY HOME MONITORING OF HAND GRIP STRENGTH IN CHRONIC INFLAMMATORY NEUROPATHIES

Pietro Emiliano Doneddu
Doneddu PE, Hadden RDM. Department of Neurology, King's College Hospital, London, UK

P3_23 A RETROSPECTIVE AUDIT OF IVIG INFUSION RATES IN THE TREATMENT OF AUTOIMMUNE NEUROLOGICAL DISEASE

Michael Cumberbatch
Cumberbatch M, Cox A. Addenbrooke's Hospital, Cambridge, UK

P3_24 SWEATING DISTURBANCES IN SENSORY NEURONOPATHY

Rodrigo Conde
(1) Conde RM, (1) Fusco T, (2) Martinez AR, (2) França MC Jr, (1) Marques Jr W, (1) Barreira AA. (1) Department of Neuroscience, University of São Paulo, Medical School of Ribeirão Preto, SP, Brazil; (2) Department of Neurology, Faculty of Medical Sciences, University of Campinas, SP, Brazil

P3_25 PURE NEURAL LEPROSY MIMIKING BRACHIAL AND LUMBOSACRAL PLEXOPATHY

Pedro José Tomaselli
(1) Tomaselli PJ, (1) Marques VD, (1) dos Santos AJC, (1) Lavigne CM, (1) Toscano PO, (1) Barreira AA, (2) Foss N, (2) Frade MA, (1, 3) Marques W Jr. (1) Division of Neuromuscular Diseases, Department of Neurosciences and Behaviour Sciences, Clinical Hospital of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; (2) Dermatology, Department of Internal Medicine, Clinical Hospital of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil; (3) Neurogenetics, Department of Neurosciences and Behaviour Sciences, University of São Paulo, Ribeirão Preto, Brazil

P3_26 CORTICOSTEROID TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY – A MULTICENTER, RETROSPECTIVE STUDY

Gwen van Lieverloo
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P3_27 DOES INTRAVENOUS IMMUNOGLOBULIN SERVE AS AN EFFECTIVE TREATMENT FOR GUILLAIN-BARRÉ SYNDROME IN DEVELOPING COUNTRIES? A CONTROLLED MATCHED PAIR ANALYSIS

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P3_28 NEOD001 DEMONSTRATES DURABLE PERIPHERAL NEUROPATHY RESPONSES IN PATIENTS WITH LIGHT CHAIN AMYLOIDOSIS AND PERSISTENT ORGAN DYSFUNCTION: RESULTS FROM A PHASE 1/2 STUDY

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P3_29 RABBIT ANTI-FGFR3 ANTIBODIES INDUCE NEURON CELL DEATH AND MODULATE FGFR3 AND NMDA AND AMPA RECEPTORS THROUGH THE P38-MAP KINASE PATHWAY

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P3_30 INTERNATIONAL CIDP OUTCOME STUDY (ICOS): A PROSPECTIVE STUDY ON CLINICAL AND BIOLOGICAL PREDICTORS OF DISEASE COURSE AND OUTCOME

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P3_31 EFFECTIVE THERAPEUTIC EFFECT OF HUMAN IMMUNOGLOBUMIN AND A RECOMBINANT Fc PORTION ON A RAT MODEL FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

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P3_32 MRI OF THE BRACHIAL PLEXUS AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: ASSESSMENT OF DTI-DERIVED MEASUREMENTS AT 3.0-T

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P3_33 EGOS DID NOT HAVE A GOOD CAPACITY TO PROGNOSIS IN GBS IN RIO GRANDE DO NORTE, BRAZIL

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P3_34 INTERNATIONAL STANDARD FOR CIDP REGISTRY AND BIOBANK, RESULTS OF THE 231ST ENMC CONSENSUS MEETING

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P3_35 VALUE OF ANTI-HNK1 ANTIBODIES IN ANTI-MAG NEUROPATHIES: AN ANALYSE OF 144 SERA

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P3_36 GBS CLASSIFICATION ACCORDING TO TWO-SETS OF EMG EXAMINATION IN A SAMPLE OF THE BRAZILIAN POPULATION

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P3_37 AUTOIMMUNE T CELLS IN AN EX VIVO MODEL OF THE PERIPHERAL NERVOUS SYSTEM

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P3_38 RANDOMIZED CONTROLLED TRIAL OF ORAL FINGOLIMOD IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (FORCIDP TRIAL): SUBGROUP ANALYSES

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P3_39 EFFICACY OF IMMUNOGLOBULINS FOR NOD B7-2 KO MICE

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P3_40 SMALL VOLUME PLASMA EXCHANGE FOR GUILLAIN-BARRE SYNDROME IN LOW INCOME COUNTRIES: A SAFETY AND FEASIBILITY STUDY

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P3_41 THE SUCCESSFUL USE OF VERY HIGH DOSE IVIG IN ACQUIRED, DEMYELINATING NEUROPATHIES- 3 CASES

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P3_42 AUTOPHAGOLYSOSOME-MEDIATED MYELIN CORPSE FORMATION BY SCHWANN CELLS IN SEGMENTAL DEMYELINATION

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P3_43 ANTIBODIES AGAINST CELL ADHESION MOLECULES AND NEURAL STRUCTURES IN PARANEOPLASTIC NEUROPATHIES

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P3_44 UPDATE ON THE INTERNATIONAL GBS OUTCOME STUDY IN CHILDREN (IGOS-KIDS)

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P3_45 HEAD AND VOICE TREMOR IMPROVING WITH IMMUNOTHERAPY IN AN ANTI-NF155 POSITIVE CIDP PATIENT

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P3_46 THE FRANCOPHONE ANTI-MAG COHORT: ANALYSIS OF THERAPEUTIC MANAGEMENT IN 202 PATIENTS

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P3_47 INHIBITION OF COMPLEMENT IN GUILLAIN-BARRÉ SYNDROME: THE ICA-GBS STUDY

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P3_48 SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF THE FCRN INHIBITOR UCB7665: A PHASE I STUDY

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P3_49 MR-NEUROGRAPHY DETECTS INVOLVEMENT OF THE PERIPHERAL NERVOUS SYSTEM IN MULTIPLE SCLEROSIS

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P3_50 IMMUNE CHECKPOINT INHIBITOR-INDUCED ACUTE NEUROPATHIES

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P3_51 ATYPICAL CASE OF ACUTE MOTOR AND SENSORY AXONAL NEUROPATHY (AMSAN) IN A PATIENT CO-INFECTED WITH SYPHILIS

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P3_52 CLINICO-ELECTROPHYSIOLOGICAL CORRELATION WITH ANTI-NEUROFASCIN155 ANTIBODY LEVELS IN THE ANTIBODY-POSITIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY PATIENTS

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P3_53 THE CHALLENGES OF ACCURATE DIAGNOSIS OF ZIKA VIRUS ASSOCIATED GUILLAIN-BARRÉ SYNDROME (GBS) IN A DENGUE ENDEMIC AREA

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P3_54 IGM ANTI-MAG PERIPHERAL NEUROPATHY: FROM PROPER ASSESSMENT TO TRIAL NEEDS (IMAGINE STUDY)

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P3_55 THE CRYPTIC 68-104 REGION OF MYELIN BASIC PROTEIN (MBP) CAUSES PAIN FROM LIGHT TOUCH EXCLUSIVELY IN FEMALE RODENTS: AUTOIMMUNE MECHANISMS OF SEXUAL DIMORPHISM IN MECHANICAL ALLODYNIA

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P3_56 GUILLAIN-BARRÉ SYNDROME – ACUTE DISEASE WITH CHRONIC CONSEQUENCES

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P3_57 MONITORING PREGNANCY IN CHARCOT-MARIE-TOOTH DISEASE: RESULTS OF A SURVEY

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P3_58 MYASTHENIA GRAVIS? MYOPATHY? OR A NEUROPATHY?

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P3_59 THE GERMAN CHARCOT-MARIE-TOOTH DISEASE NETWORK (CMT-NET): FROM RISK FACTORS TO THERAPEUTIC ACTIONS

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P3_60 RELEVANCE AND FREQUENCY OF DIFFERENT TYPES OF CHARCOT-MARIE-TOOTH NEUROPATHY IN A LARGE POPULATION OF PATIENTS STUDIED AT A SINGLE CLINICAL SITE

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P3_61 THE INHERITED NEUROPATHY VARIANT BROWSER

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P3_62 AN ONGOING PHASE 2 STUDY EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ACE-083 IN PATIENTS WITH CMT1 AND CMTX

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P3_63 AUTONOMIC SYMPTOMS IN TRANSTHYRETIN AMYLOIDOSIS: AN ANALYSIS OF SYMPTOMATIC SUBJECTS FROM THE THAOS REGISTRY

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P3_64 NOVEL, LIKELY PATHOGENIC, SEQUENCE VARIANTS IN HEREDITARY NEUROPATHY GENES

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P3_65 CMT2 WITH PYRAMIDAL TRACT INVOLVEMENT DUE TO ARG329HIS MUTATION IN ALANYL-TRNA SYNTHETASE (AARS)

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P3_66 UNRAVELLING THE DISEASE MECHANISMS UNDERLYING THE DHMN1 INSERTION

Anthony Cutrupi
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P3_67 HUMAN MOTOR NEURON NEUROSPHERES AS A NEW PLATFORM TO STUDY AXONAL PHENOTYPES IN PERIPHERAL NEUROPATHIES

Renata de Moraes Maciel dos Santos
(1, 2) de Moraes Maciel Renata, (1,2) Saporta Mario A (1) Department of Neurology, University of Miami Miller School of Medicine, Miami, FL, USA; (2) Department of Human Genetics, Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA

P3_68 AXONAL NEUROPATHIES DUE TO MUTATIONS IN SMALL HEAT SHOCK PROTEINS: CLINICAL, GENETIC AND FUNCTIONAL INSIGHTS INTO NOVEL MUTATIONS

Andoni Echaniz-Laguna
(1) Echaniz-Laguna A, (2) Geuens T, (3) Petiot P, (4) Péréon Y, (2) Adriaenssens E, (2) Haidar M, (2) Capponi S, (5)

Maisonobe T, (5) Fournier E, (5) Dubourg O, (5) Degos B, (5) Salachas F, (5) Lenglet T, (5) Eymard B, (6) Delmont E, (7) Pouget J, (8) Morales Juntas R, (9) Goizet C, (3) Latour P, (2) Timmerman V, (5) Stojkovic T. (1) Strasbourg University Hospital, Strasbourg, France; (2) Peripheral Neuropathy Group, VIB Department of Molecular Genetics and Institute Born Bunge, University of Antwerp, Antwerpen, Belgium (3) Lyon University Hospital, Lyon, France; (4) Nantes University Hospital, Nantes, France; (5) Hôpital de la Pitié-Salpétrière, Paris, France; (6) Nice University Hospital, Nice, France; (7) Marseille University Hospital, Marseille, France; (8) Montpellier University Hospital, Montpellier, France; (9) Bordeaux University Hospital, Bordeaux, France

P3_69 MUTATIONS IN BAG3 CAUSE ADULT ONSET CHARCOT MARIE TOOTH DISEASE

Shawna Feely

(1) Feely S, (2) Rebelo A, (2) Abreu L, (2) Tao F, (1) Bacon C, (2) Zuchner S, (1) Shy ME. (1) University of Iowa, Iowa City IA; (2) Dr. John T Macdonald Department of Human Genetics and Hussman Institute for Human Genetics, Miller School of Medicine, University of Miami, Miami FL

P3_70 SCHWANN CELL AND ENDOTHELIAL CELL DAMAGE IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

Haruki Koike

(1) Koike H, (1) Ikeda S, (1) Takahashi M, (1) Kawagashira Y, (1) Iijima M, (2) Misumi Y, (2) Ando Y, (3) Ikeda SI, (1) Katsuno M, (1) Sobue G (1) Nagoya University Graduate School of Medicine, Nagoya, Japan; (2) Kumamoto University, Kumamoto, Japan; (3) Shinshu University Hospital, Matsumoto, Japan

P3_71 MOTOR AXON EXCITABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1B WITH A NULL MUTATION IN THE P0 GENE – INSIGHTS FORM A MOUSE MODEL

Christian Krarup

(1,2) Krarup C, (1,2) Moldovan M, (1) Alvarez S, (3) Ciano C, (3) Pisciotta C, (3) Pareyson D. (1) Univ. of Copenhagen, Copenhagen, Denmark; (2) Rigshospitalet, Copenhagen, Denmark; (3) Fondazione IRCCS Istituto Neurologico C.Besta, (INCB), Milan, Italy

P3_72 ACE-083, A LOCALLY-ACTING GDF/ACTIVIN LIGAND TRAP, AUGMENTS DORSIFLEXOR MUSCLE FUNCTION IN A MURINE MODEL OF CHARCOT-MARIE-TOOTH (CMT) DISEASE

Jia Li

Li J, Cannell M, Suragani R, Pearsall R, Kumar R. Acceleron Pharma Inc, Cambridge, USA

P3_73 SENSITIVITY OF THE CMT INFANT SCALE: PRELIMINARY ANALYSIS OF CMT SUBTYPES AND COMPARISON TO CONTROLS

Melissa Mandarakas

(1,2) Mandarakas M, (3) Shy R, (4) Kennedy R, (2) Herbert K, (1,2) Rose K, (1,2) Menezes MP, (4) Ryan M, (4) Yiu E, (2) Farrar M, (2) Sampaio H, (5) Estilow T, (6) Moroni I, (5) Yum S, (7) Finkel R, (8) Acsadi G, (9) Eichinger K, (10) Laura M, (10) Reilly MM, (11) Muntoni F, (1) Refshauge K, (3) Shy M, (1,2) Burns J, (12) Sanmaneechai O for the Inherited Neuropathies Consortium. (1) University of Sydney, Sydney, Australia; (2) Sydney Children's Hospitals Network (Randwick and Westmead), New South Wales, Australia; (3) University of Iowa Hospitals and Clinics, Iowa City, USA; (4) The Royal Children's Hospital and University of Melbourne, Victoria, Australia; (5) The Children's Hospital of Philadelphia, Philadelphia, USA; (6) Istituto Neurologico Carlo Besta, Milan, Italy; (7) Nemours Children's Hospital, Orlando, USA; (8) Connecticut Children's Medical Center, Hartford, USA; (9) University of Rochester, Rochester, USA; (10) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London, UK; (11) Great Ormond Street Hospital, London, UK; (12) Siriraj Hospital, Mahidol University, Bangkok, Thailand

P3_74 CLINICAL AND NEUROPHYSIOLOGICAL PROFILE OF CMTX3 IN CHILDHOOD

Manoj Menezes

(1) Kanhangad M, (2,3) Cornett K, (2,4) Brewer MH, (2,4,5) Nicholson GA, (1,2,3) Ouvrier RA, (6,7,8) Ryan MM, (9) Smith RL, (9) Subramanian GM, (2,10) Young HK, (2,4,5) Kennerson ML, (2,3,11) Burns J, (1,2,3) Menezes MP.(1) T.Y. Nelson Department of Neurology and Neurosurgery, The Children's Hospital at Westmead, Westmead, Australia; (2) University of Sydney, Camperdown, Australia; (3) Institute for Neuroscience and Muscle Research, The Children's Hospital at Westmead, Westmead, Australia; (4) Northcott Neuroscience Laboratory, ANZAC Research Institute, Concord, Australia; (5) Molecular Medicine Laboratory, Concord Repatriation General Hospital, Concord, Australia; (6) Department of Neurology, Royal Children's Hospital, Parkville, Australia: (7) Murdoch Childrens Research Institute, Parkville, Victoria, Australia; (8) Department of Paediatrics, University of Melbourne, Parkville, Australia; (9) Department of Neurology, John Hunter Children's Hospital, and University Faculty of Health, Newcastle, Australia; (10) Department of Paediatrics, Royal North Shore Hospital, St Leonards, Australia; (11) Paediatric Gait Analysis Service of New South Wales, Sydney Children's Hospitals Network (Randwick and Westmead), Australia

P3_75 CMT1B AND SENSORY ABNORMALITIES ASSOCIATED WITH A MPZ NULL MUTATION

Giuseppe Piscosquito
(1) Piscosquito G, (2) Saveri P, (1) Provitera V, (1) Stancanelli A, (3) Ciano C, (4) Magri S, (4) Taroni F, (5) Fabrizi GM (1) Nolano M, (2) Pareyson D. (1) Neurorehabilitation Unit, "Maugeri" Scientific Clinical Institutes, Scientific Institute of Telese Terme (BN), Italy; (2) Unit of Rare Neurological Diseases of Adulthood, Department of Clinical Neurosciences, IRCCS Foundation, "C. Besta" Neurological Institute, Milan, Italy; (3) Neurophysiopathology and Epilepsy Centre, Department of Diagnostics and Applied Technology, IRCCS Foundation, C. Besta Neurological Institute, Milan, Italy; (4) Unit of Genetics of Neurodegenerative and Metabolic Disease, Department of Diagnostic and Applied Technology, IRCCS Foundation, "C. Besta" Neurological Institute, Milan, Italy; (3) Section of Neuropathology, Department of Neurological and Movement Sciences, University of Verona, Verona, Italy

P3_76 EVALUATING THE BENEFITS OF COMMUNITY BASED AEROBIC TRAINING ON THE PHYSICAL HEALTH AND WELL- BEING OF PEOPLE WITH CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: A PILOT RANDOMISED CONTROLLED TRIAL

Gita Ramdharry
Wallace A (1), Pietrusz A (1), Dewar E (1), Dudziec M (1,2), Jones K (1), Hennis P (3), Sterr A (4), Baio G (5), Butcher K (6), Laura M (1), Skorupinska I (1), Skorupinska M (1), Trenell M (7), Hanna MG (1), Reilly MM (1), Ramdharry GM (1,2). (1) MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, UK (2) Faculty of Health, Social Care & Education, Kingston University/St George's University of London, UK (3) Institute of Sport, Exercise and Health, UCL, UK (4) Department of Psychology, University of Surrey, Guildford, UK (5) Department of Statistical Science, UCL, London. UK (6) Charcot Marie Tooth United Kingdom, Registered charity number 1112370, UK (7) Movelab, Newcastle University, UK

P3_77 RECESSIVE SH3TC1 VARIANTS IN A CASE WITH PROGRESSIVE AND LETHAL PERIPHERAL DEMYELINATION

Adriana Rebelo
(1) Rebelo A, (2) Feely, SM, (1) Bis D, (1) Tao F, (2) Shy, R, (1) Zuchner, S, (2) Shy, M. (1) Dr. John T. Macdonald Foundation Department of Human Genetics, John P. Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, USA; (2) Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, USA

P3_78 CHARCOT-MARIE-TOOTH DISEASE TYPE-1A (CMT1A) PLUS

Megan Simmons
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P3_79 MOTOR UNIT NUMBER INDEX CORRELATES WITH DISABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

Joachim Bas
(1) Bas J, (1, 2) Delmont E, (1) Fatehi F, (3) Boulay C, (3) Chabrol B, (1, 5) Salort-Campana E, (1) Sévy A, (1) Verschueren A, (1, 5) Pouget J, (4) Lefebvre MN, (1) Grapperon AM, (1, 5) Attarian S. (1) Reference Center for Neuromuscular Diseases and ALS, La Timone University, Aix-Marseille University, Marseille, France; (2) Aix-Marseille University, UMR 7286, Medicine Faculty, Marseille, France; (3) Reference Center for Pediatric Neuromuscular Disorders, La Timone University Hospital, Aix-Marseille University, Marseille, France; (4) CIC-CPCET, La Timone University Hospital, Aix-Marseille University, Marseille, France; (5) Aix-Marseille University, Inserm, GMGF, Marseille, France

P3_80 PHENOTYPICAL AND GENOTYPICAL CROSSROADS BETWEEN INHERITED DISEASES OF NERVE AND MUSCLE: TWO EXAMPLES OF VCP AND GNE –RELATED DISORDERS

Gian Maria Fabrizi
(1) Fabrizi GM, (1) Testi S, (2) Høyer H, (2) Braathen Gj, (3) Squintani G, (1) Bertolasi L, (1) Ferrarini M, (1) Taioli F, (1) Cabrini I, (1) Pancheri E, (1) Cavallaro T, (1) Tonin P. (1) Department of Neuroscience, Biomedicine and Movement, University of Verona and Department of Neuroscience, AOUI Verona, Italy; 2) Section of Medical Genetics, Department of Laboratory Medicine, Telemark Hospital, Skien, Norway

P3_81 PMP22 EXON 4 DELETION CAUSES ER RETENTION OF PMP22 AND A GAIN-OF-FUNCTION ALLELE IN CMT1E

Tiffany Grider
(1) Wang D,* (1) Wu X,* (1) Bai Y, (3) Zaidman C, (1, 2) Grider T, (2) Kamholz J, (4) Lupski JR, (3) Connolly AM, and (1, 2)Shy ME(1) Department of Neurology, Neuromuscular Division, University of Iowa Hospitals and Clinics, Iowa City, Iowa (2) Department of Neurology, Neurogenetics Division, University of Iowa Hospitals and Clinics, Iowa City, Iowa (3) Departments of Neurology and Pediatrics, Washington University School of Medicine, Neuromuscular Division, St. Louis MO (4) Department of Pediatrics, Baylor College of Medicine, Houston, Texas, United States

P3_82 TAFAMIDIS DELAYS DISEASE PROGRESSION COMPARABLY ACROSS VAL30MET AND NON-VAL30MET GENOTYPES IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

Denis Keohane
(1) Gundapaneni B, (2) Sultan MB, (2) Keohane DJ, (2) Schwartz J. (1) inVentiv Health Inc., Burlington, MA, USA; (2) Pfizer Inc, New York, NY, USA

P3_83 THE DEVELOPMENT OF NEUROPATHY IN A MOUSE MODEL OF CMT2E - SEQUENTIAL NERVE CONDUCTIONS

Eunjoo Lancaster
(1) Lancaster E, (1) Li J, (2) Liem R (1) Scherer SS. (1) Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA; (2) Columbia University School of Medicine, New York, NY, USA

P3_84 MOLECULAR DIAGNOSIS OF INHERITED PERIPHERAL NEUROPATHIES: GENE PANEL VS. EXOME SEQUENCING

Vincenzo Lupo
(1,2) Lupo V, (3,4) Frasquet M, (1,2) Sánchez-Monteagudo A, (3) Barreiro M, (5) García-Romero M, (6) Alberti MA, (7) Márquez-Infante C, (5) Pascual SI, (6) Casasnovas C, (4,8,9) Quintans B, (10) Camacho A, (10) Domínguez C, (11) Sedano MJ, (11) Pelayo AL, (12) Pardo J, (12) Sobrino T, (4,8,9) Sobrido MJ, (3,4) Sevilla T, (1,2) Espinós C. (1) Centro de Investigación Príncipe Felipe, Valencia, Spain; (2) INCLIVA & IIS La Fe Rare Diseases Joint Units, Valencia, Spain; (3) Hospital Universitari i Politècnic La Fe, Valencia, Spain; (4) CIBER of Rare Diseases (CIBERER); (5) Hospital La Paz, Madrid, Spain; (6) Hospital Bellvitge, Barcelona, Spain; (7) Hospital Virgen del Rocio, Sevilla, Spain; (8) Instituto de Investigaciones Sanitarias (IDIS), Santiago de Compostela, Spain; (9) Fundación Pública Galega de Medicina Xenómica, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain; (10) Hospital 12 de Octubre, Madrid, Spain; (11) Hospital Universitario Marqués de Valdecilla, Santander, Spain; (12) Hospital Clínico Universitario Santiago de Compostela, Santiago de Compostela, Spain

P3_85 CLINICAL SIGNIFICANCE OF CONDUCTION BLOCK IN CMT1A PATIENTS WITH PMP22 DUPLICATION

Jihyung Park
(1) Park J, (2) Choi MS, (3) Seok JM, (4) Min JH, (5) Kim BJ, (6) Choi BO. (1) Samsung Medical Center, Seoul, Korea, Republic of; (2) Samsung Medical Center, Seoul, Korea, Republic of; (3) Samsung Medical Center, Seoul, Korea, Republic of; (4) Samsung Medical Center, Seoul, Korea, Republic of; (5) Samsung Medical Center, Seoul, Korea, Republic of; (6) Samsung Medical Center, Seoul, Korea, Republic of

P3_86 CHARCOT MARIE TOOTH DISEASE TYPE 2 (CMT2P) DUE TO LRSAM1 MUTATIONS: CLINICAL AND GENETIC FINDINGS

Andrea Cortese
(1) Cortese A, (1) Laura M, (2) Polke H, (2) Poh R, (1) Rossor AM, (1) Tomaselli P, (1) Blake J, (1) Lunn M, (3) Houlden H, (1) Reilly MM. (1) MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, Queen Square, London, UK; (2) Department of Neurogenetics, The National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK; (3) Department of Molecular Neuroscience, UCL Institute of Neurology and the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

P3_87 DIFFERENT AXONAL DYSFUNCTION PATTERN IN SEROPOSITIVE AND SERONEGATIVE SJÖGREN'S SYNDROME

Jowy Tani
(1,2) Jowy Tani, (3) Hsien-Tzung Liao, (4) Hui-Ching Hsu, (4) Lung-Fang Chen, (5) Cindy Shin-Yi Lin, (6) Tsui-San Chang, (1,6) Jia-Ying Sung. (1)Department of Neurology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; (2)Ph.D. Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University and National Health Research Institutes; (3) Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; (4) Division of Allergy, Immunology and Rheumatology, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan; (5) Translational Neuroscience, Department of Physiology, School of Medicine Science, Faculty of Medicine, University of New South Wales, Sydney, Australia; (6)Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

WEDNESDAY 12 JULY 2017

7.30 - 8.30 **Clinical Trial Updates** AUDITORIUM

Poster Session 4 Viewing TRAMUNTANA FOYER

(see end of Wednesday 12 July 2017 for poster titles)

Coffee TRAMUNTANA HALL

Plenary Lecture and Platform Session 6

Chairs: **Hugh Willison** and **H. Stephan Goedee**

8.30 - 9.00 **Plenary 6** AUDITORIUM

NEURO-EPIDEMIOLOGY AND ITS RELEVANCE TO PHERIPHERAL NEUROPATHY

James J. Sejvar

9.00 - 10.00 **Platform Session 6** AUDITORIUM

9.00 **O7_1**

INTERNATIONAL GUILLAIN-BARRÉ SYNDROME OUTCOME STUDY (IGOS): DESCRIPTION OF THE FIRST 1000 PATIENTS

Bianca van den Berg

(1) van den Berg B, (1) Verboon C, (1) Doets A, (2) Chavada G, (2) Davidson A, (2) Willison HJ, (3) Harbo T, (4) Gorson KC, (5) Hartung HP, (6) Lehmann HC6, (7) Kusunoki S, (8) Querol L, (8) Illa I, (9) Nobile-Orazio E, (10) Reisin RC, (11) Reddel SW, (12) Islam Z, (13) Islam B, (14) Deen Mohammad Q, (15) Van den Bergh P, (16) Feasby TE, (17) Péréon Y, (18) Shahrizaila N, (19) Hsieh ST, (20) Bateman K, (21) Dardiotis E, (22) Wang Y, (1) van Doorn PA, (23) Hughes RAC, (24) Cornblath DR and (1, 25) Jacobs BC, the IGOS Consortium. (1) Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands; (2) Department of Neurology, University of Glasgow, Glasgow, UK; (3) Department of Neurology, Aarhus University Hospital, Aarhus, Denmark; (4) Department of Neurology, Tufts University School of Medicine, Boston, USA; (5) Department of Neurology, University of Düsseldorf, Düsseldorf, Germany; (6) Department of Neurology, University Hospital of Cologne, Köln, Germany; (7) Department of Neurology, Kindai University Faculty of Medicine, Osaka, Japan; (8) Department of Neurology, Hospital Sant Pau, UAB, Ciberer, Barcelona, Spain; (9) Department of Neurology, Milan University, Humanitas Istitute, Milan, Italy; (10) Department of Neurology, Hospital Britanico, Buenos Aires, Argentina; (11) Department of Neurology, Concord Repatriation General Hospital, Sydney, Australia; (12) Department of Neurology, ICDDR,B, Dhaka, Bangladesh; (13) Laboratory Sciences and Services Division, ICDDR,B, Dhaka, Bangladesh; (14) National Institute of Neuroscience and Hospital, Dhaka, Bangladesh; (15) Department of Neurology, University Hospital St. Luc, Brussels, Belgium; (16) Department of Clinical Neuroscience, University of Calgary, Calgary, Canada; (17) Reference Centre for Neuromuscular Diseases, Nantes University Hospital, Nantes, France; (18) Department of Neurology, University of Malaya, Kuala Lumpur, Malaysia; (19) Department of Neurology, National Taiwan University Hospital, Taipei, Taiwan; (20) Department of Neurology, University of Cape Town, Cape Town, South Africa; (21) Department of Neurology, University of Thessaly, Larissa Thessaly, Greece; (22) Department of Neurology, Affiliated Hospital of Jining Medical College, Jining, China; (23) Department of Neurology, Institute of Neurology, University College, London, UK; (24) Department of Neurology, Johns Hopkins University, Baltimore, USA; (25) Department of Immunology, Erasmus Medical Centre, Rotterdam, The Netherlands

9.15 **O7_2**

REFINEMENT OF DIAGNOSTIC CRITERIA FOR CIDP BEYOND ELECTROPHYSIOLOGY: DATA FROM THE ITALIAN DATABASE FOR THE DIAGNOSIS AND THERAPY OF CIDP AND VARIANTS

Giuseppe Liberatore

(1) Liberatore G, (2) Cocito D, (3) Fazio R, (4) Santoro L, (5) Filosto M, (6) Mazzeo A, (7) Jann S, (8) Cortese A, (9) Carpo M, (10) Clerici M, (11) Luigetti M, (12) Lauria G, (13) Fierro B, (14) Antonini G, (15) Cavaletti G, (16) Rosso T, (17) Benedetti L, (18) Briani C, (19) Marfia G, (1) Doneddu P, (2) Peci E, (3) Velardo D, (4) Manganelli F, (5) Todeschini A, (6) Toscano A, (7) Verrengia EP, (8) Piccolo L, (1) Nobile-Orazio E. (1)Milan University, IRCCS Humanitas Clinical and Research Center, Milan, Italy (2)Città della Salute e della Scienza Hospital, Torino, Italy (3)IRCCS San Raffaele Hospital, Milan, Italy (4)Università degli Studi di Napoli "Federico II", Naples, Italy (5)University of

Brescia, Spedali Civili Hospital, Brescia, Italy (6)Azienda Ospedaliera Universitaria "G. Martino," Messina, Italy (7)Niguarda Cà Granda Hospital, Milan, Italy (8)IRCCS Fondazione Mondino, Pavia, Italy (9)Treviglio Hospital, Treviglio, Italy (10)Fondazione Macchi Hospital, Varese, Italy (11)Università Cattolica del Sacro Cuore, Rome, Italy (12)IRCCS Carlo Besta Neurological Institute, Milan, Italy (13)Azienda Ospedaliera Universitaria Policlinico Paolo Giaccone, Palermo, Italy (14)Sant'Andrea Hospital, Univesity of Rome, Rome, Italy (15)Milano Bicocca University, Monza, Italy (16)Azienda UL.SS. 8 Asolo, Castelfranco Veneto, Italy (17)Ospedale Sant'Andrea, La Spezia, Italy (18)Università di Padova, Padua, Italy (19)Policlinico Tor Vergata, Rome, Italy

9.30 **O7_3**

THE ROLE OF IMMUNE CELLS IN NERVE DEGENERATION AND REGENERATION: A NEW PERSPECTIVE

Richard Zigmond

Lindborg JA, Niemi, JP, DeFrancesco A, Zigmond RE. Case Western Reserve University, Cleveland, USA

9.45 **O7_4**

PREDICTORS OF SEVERITY AND OUTCOME OF GUILLAIN-BARRÉ SYNDROME IN CHILDREN

Joyce Roodbol

(1,2) Roodbol J, (5) Korinthenberg R, (2) de Wit MCY, (4) Lingsma H, (2) Catsman-Berrevoets CE, (1,3) Jacobs BC. (1) Department of Neurology, (2) Paediatric Neurology, (3) Immunology, (4) Public health, Erasmus MC– Sophia Children's Hospital, University Medical Center Rotterdam, The Netherlands. (5) Division of Neuropaediatrics and Muscular Disorders, Department of paediatrics and Adolescent Medicine, University Hospital Freiburg, Freiburg, Germany

10.00 - 10.30 Coffee **TRAMUNTANA HALL**

10.30 - 12.00 Oral Poster Presentations Session 6 AUDITORIUM

Chairs: **Bart Jacobs** and **Gwen Van Lieverloo**

OP6_1 IMMUNOGLOBULIN TREATMENT FOR PATIENTS WITH MILD GUILLAIN-BARRÉ SYNDROME: AN INTERNATIONAL PROSPECTIVE OBSERVATRIONAL STUDY

Christine Verboon

(1) Verboon C and (1, 2) Jacobs BC, the IGOS Consortium, (1) Department of Neurology, Erasmus Medical Centre, Rotterdam, The Netherlands, (2) Department of Immunology, Erasmus Medical Centre, Rotterdam, The Netherlands

OP6_2 MUTIPLE SITES NERVE ULTRASOUND OF CHARCOT-MARIE-TOOTH TYPE 1A AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Minsheng Liu

Niu JW, Cui LY, Liu MS. The Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China

OP6_3 CIDP DIAGNOSTIC CRITERIA AND TREATMENT RESPONSE

Mamatha Pasnoor

Pasnoor M, Roach C, Barohn RJ, Statland J, Jawdat O, Dick A, Glenn M, Dimachkie MM. Department of Neurology, Neuromuscular Division, The University of Kansas Medical Center, Kansas City, KS, USA

OP6_4 PROPOSAL OF DIAGNOSTIC CRITERIA FOR POEMS SYNDROME WITH THE HIGH SENSITIVITY/ SPECIFICITY

Tomoki Suichi

(1) Suichi T, (1) Misawa S, (2) Sato Y, (1) Beppu M, (1) Sekiguchi Y, (1)Shibuya K, (1) Watanabe K, (1) Amino H, (1) Kuwabara S. (1) Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan; (2) Clinical Research Center, Chiba University Hospital, Chiba, Japan

OP6_5 BLINK R1 LATENCY UTILITY IN DIAGNOSIS AND TREATMENT ASSESSMENT OF POEMS AND CIDP

Wei Wang

(1, 2) Wang W, (1) Litchy WJ, (1) Mauermann ML, (1) Dyck PJB, (3) Dispenzieri A, (4) Mandrekar J, (1) Dyck PJ, (1) Klein CJ. (1) Department of Neurology, Mayo Clinic, Rochester MN, USA; (2) Department of Neurology, China-Japan Friendship Hospital, Beijing, China; (3) Department of Hematology, Mayo Clinic, Rochester MN, USA; (4) Biomedical Statistics and Informatics, Mayo Clinic, Rochester MN, USA

OP6_6 ITG2A-EXPRESSING SCHWANN CELLS UPREGULATE A MACROPHAGE RECRUITMENT FACTOR PERIOSTIN DURING SPONTANEOUS AUTOIMMUNE PERIPHERAL NEUROPATHY

Denise Elena Allard
(1) Allard D, (2) Zeng XL, (3) Wang Y, (4) Kimpston C, (5) Notini R, (6) Li J, (7) Sailer D, (8) Conley B, (9) Howard J, (10) Scherer S, (11) Su M. (1) University of North Carolina Department of Pediatrics, Chapel Hill, United States of America; (2) University of North Carolina Department of Neurology, Chapel Hill, United States of America; (3) University of Pennsylvania Department of Neurology, Philadelphia, United States of America

OP6_7 HIGH INCIDENCE OF GUILLAIN-BARRÉ SYNDROME AFTER ZIKA VIRUS INFECTION IN THE STATE RIO GRANDE DO NORTE, IN NORTHEAST BRAZIL

Mário Emílio Dourado
Dourado ME, Fernandes U, Vital AL, Ramos E, Urbano JC, Sena A, Fraiman PHA,Luz K, Queiroz JW, Jeronimo SMB. Federal University of Rio Grande do Norte, Natal, Brazil

OP6_8 DIFFERENCES OF ANTIBODY REACTIVITIES AGAINST GLYCOLIPID COMPLEXES AMONG GUILLAIN-BARRÉ SYNDROME, MILLER FISHER SYNDROME AND BICKERSTAFF BRAINSTEM ENCEPHALITIS

Yoshikawa Keisuke
Keisuke Y, Miyuki M, Motoi K, Susumu K. Department of Neurology, Kindai University Faculty of Medicine, Osaka, Japan

OP6_9 INTERNATIONAL ZIKA VIRUS RELATED GUILLAIN-BARRÉ SYNDROME OUTCOME STUDY (IGOS-ZIKA): A CASE- CONTROLLED STUDY

Sonja Leonhard
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OP6_10 THE DIAGNOSTIC YIELD OF PCR-BASED CLONALITY TESTING ON NERVE BIOPSY IN THE DIAGNOSIS OF NEUROLYMPHOMATOSIS

Laurent Magy
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OP6_11 INTRAVENOUS IMMUNOGLOBULIN (IVIG) FOR RESTABILIZATION TREATMENT AFTER IVIG WITHDRAWAL IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP). RESULTS FROM THE PRE- RANDOMIZATION PHASE OF THE PATH STUDY

Orell Mielke
(1) Mielke O, (2) Bril V, (3) van Geloven N, (4) Hartung H-P, (5) Lewis RA, (6) Sobue G, (1) Lawo J-P, (1) Durn BL, (7) Cornblath DR, (8) Merkies ISJ, (9) van Schaik IN, on behalf of the PATH study group. (1) CSL Behring, Marburg, Germany and King of Prussia, PA, USA; (2) Department of Medicine (Neurology), University Health Network, University of Toronto, Toronto, Canada; (3) Department of Biostatistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands; (4) Department of Neurology, Heinrich Heine University, Düsseldorf, Germany; (5) Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; (6) Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya, Japan; (7) Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; (8) Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands; (9) Department of Neurology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

OP6_12 ELECTROPHYSIOLOGICAL CRITERIA FOR GBS SUBTYPE DIAGNOSIS: A PROSPECTIVE MULTICENTRIC EUROPEAN STUDY

Peter Van den Bergh

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OP6_13 LARGE COVERAGE MR NEUROGRAPHY IN CIDP – DIAGNOSTIC ACCURACY AND ELECTROPHYSIOLOGICAL CORRELATION

Min-Suk Yoon

(1) Kronlage M, Baeumer P, (2) Pitarokoili K, (1) Schwarz D, (1) Schwehr V, (1) Godel T, (1) Heiland S, (2) Gold R, (1) Bendszus M, (2) Yoon MS. (1) Heidelberg University Hospital, Department of Neuroradiology, Germany (2) St. Josef. Hospital, Ruhr University of Bochum, Department of Neurology, Germany

OP6_14 MODELLING THE PHARMACOKINETICS OF INTRAVENOUS IMMUNOGLOBULIN IN GUILLAIN-BARRÉ SYNDROME

Willem Jan Fokkink

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OP6_15 ANTIBODIES AGAINST THE NODE OF RANVIER, A FLOW CYTOMETRY ANALYSIS

Emilien Delmont

(1)Kouton L, (2)Kremer L, (3)Tard C, (4) Morales R, (5) Kuntzer T, (1)Attarian S, (6)Boucraut J, (1)Delmont E (1) Referral centre for ALS and neuromuscular diseases, Marseille, France (2) Neurology department, Strasbourg, France (3) Neurology department, Lille, France (4) Neurology department, Montpellier, France (5) Neurology department, Lausanne, Switzerland (6) Immunology laboratory, Marseille, France

12.00 - 14.00 **PNS Board Meeting 2** MESTRAL 1 ROOM
(Only Board Members are invited)

12.00 - 14.00 **Poster Viewing** TRAMUNTANA FOYER

12.00 - 14.00 Lunch

Poster Session 4 TRAMUNTANA FOYER

P4_1 PATIENT ASSISTED INTERVENTION FOR NEUROPATHY: COMPARISON OF TREATMENT IN REAL LIFE SITUATIONS (PAIN-CONTROLS)

Richard Barohn

(1) Barohn RJ, (1) Gajewski B, (1) Pasnoor M, (1) Brown L, (1) Herbelin L, (1) Kimminau K, (1) Jawdat O, (1) Parks C, (1) Shlemon P, (1) Dimachkie MM, and the PAIN-CONTROLs Study Team (1). The University of Kansas Medical Center, Kansas City, KS, USA

P4_2 DIGIT WRINKLE SCAN©: FROM NORMATIVE VALUES TO ITS CLINICAL APPLICABILITY IN SMALL FIBER NEUROPATHY

Isis Joosten

(1) Joosten IBT, (1) Sopacua M, (1) Bovenkerk DSH, (1) Potten RMM, (1) Faber CG, (2)Merkies ISJ, (1) Hoeijmakers JGJ. (1) Maastricht University Medical Center, Maastricht, The Netherlands; (2) St. Elisabeth Hospitaal, Willemstad, Curaçao

P4_3 COMPARISON BETWEEN COMPLEX REGIONAL PAIN SYNDROME TYPE 1 AND 2 BASED ON ELECTROPHYSIOLOGIC, IMAGING AND CLINICAL FINDINGS

Je-Young Shin
(1) Shin JY, (2) Moon JY. (3) Sung JJ. (1) Seoul National University Hospital, Seoul, Republic of Korea; (2) Seoul National University Hospital, Seoul, Republic of Korea; (3) Seoul National University Hospital, Seoul, Republic of Korea

P4_4 PERIPHERAL ANTINOCICEPTIVE EFFECT OF VENLAFAXINE IN RATS

Gülay Sezer
(1) Sezer G, (2) Tekol Y, (2,3) Sezer Z. (1) Erciyes University, Betül Ziya Eren Genome and Stem Cell Centre, Kayseri, Turkey, (2) Erciyes University, School of Medicine, Pharmacology Department, Kayseri, Turkey. (3) Erciyes University, Good Clinical Practice and Research Centre, Kayseri, Turkey

P4_5 NEUROPHYSIOLOGICAL MEASURES CORRELATE WITH PATIENT REPORTED SYMPTOMS OF CHEMOTHERAPY- INDUCED PERIPHERAL NEUROPATHY

Hannah Timmins
(1) Timmins HC, (1) Li T, Kiernan MC (1), (2, 3, 4) Horvath LG, (2) Harrison M, (2, 3) Grimison P, (2, 6) Cox KM, (3, 5) Boyle FM, (7, 8) Goldstein D, (1). Park SB. (1) Brain and Mind Centre, University of Sydney; (2) Chris O'Brien Lifehouse, Sydney, NSW, Australia; (3) Sydney Medical School, University of Sydney, NSW, Australia; (4) Department of Oncology, Royal Prince Alfred Hospital, NSW, Australia; (5) Patricia Ritchie Centre for Cancer Care and Research, The Mater Hospital, NSW Australia; (6) Sydney Nursing School, University of Sydney, NSW, Australia; (7) Prince of Wales Clinical School, UNSW, NSW, Australia; (8) Department of Medical Oncology at Prince of Wales Hospital, Sydney, NSW, Australia.

P4_6 IVIg EFFECT IN A WISTAR RAT MODEL OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

Elisa Ballarini
(1) Ballarini E, (1) Meregalli C, (1) Carozzi V, (1) Chiorazzi A, (1) Canta A, (2) Monza L, (3) Fumagalli G, (3) Pozzi E, (1-3) Alberti P, (1) Rodriguez-Menendez V, (1) Bossi M, (4) Marjanovic I, (4) Scali C, (1) Marmiroli P, (1) Cavaletti G. (1) School of Medicine and Surgery, Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy; (2) PhD program in Translational and Molecular Medicine, DIMET, University of Milano-Bicocca, Milano, Italy; (3) PhD program in Neuroscience, University of Milano-Bicocca, Monza, Italy; (4) Kedrion S.p.A., Loc. Ai Conti, Castelvecchio Pascoli (Barga) Lucca, Italy

P4_7 CHARACTERIZATION OF A TRANSGENIC MOUSE MODEL OVEREXPRESSING TNF ALPHA IN MYELINATING SCHWANN CELLS

Belén García-Lareu
(1 2 3) García-Lareu B, (2) Ariza L, (1 4) Cobianchi S, (1 2 5 6) Chillón M, (1 3 4) Navarro X, (1 2 3) Bosch A. (1) Institut de Neurociències, (INc), UAB, Barcelona, Spain; (2) Departament de Bioquímica i Biologia Molecular, UAB, Barcelona, Spain; (3) Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas (CiberNed), Insituto de Salud Carlos III, Madrid, Spain; (4) Departament Biologia Cel·lular, Fisiologia i Immunologia, UAB, Barcelona, Spain; (5) Institut Català de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; (6) Unitat Mixta UAB-VHIR, Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain

P4_8 DIAGNOSTIC VALUE OF SYMPTOMS IN CHRONIC POLYNEUROPATHY: THE ERASMUS POLYNEUROPATHY SYMPTOM SCORE (E-PSS)

Rens Hanewinckel
(1, 2) Hanewinckel R, (1) van Oijen M, (3, 4) Merkies ISJ, (5) Notermans NC, (5) Vrancken AFJE, (2) Ikram MA, (1) van Doorn PA. (1) Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands; (2) Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands; (3) Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands; (4) Department of neurology, St. Elisabeth Hospital, Willemstad, Curaçao; (5) Department of Neurology, University Medical Center Utrecht, the Netherlands

P4_9 LONG-TERM OUTCOME OF INTRAEPIDERMAL NERVE FIBER REGERNATION IS IMPAIRED IN DIABETIC PATIENTS, BUT IS INDEPENDET OF AXON LENGTH OR BLOOD GLUCOSE LEVEL

Mohammad Khoshnoodi
Khoshnoodi M, Truelove S, Polydefkis M. The Johns Hopkins University, Baltimore, MD

P4_10 A NOVEL PROTEIN, MAJOR URINARY PROTEIN (MUP) CONTRIBUTES TO THE BEHAVIOUR OF DIABETIC AND NONDIABETIC SENSORY NEURONS

Trevor Poitras
Poitras T, Chandrasekhar A, Singh V, Martinez J, Zochodne DW. Neuroscience Mental Health Institute, and Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada T6G 2R3

P4_11 INHIBITION OF HISTONE DEACETYLASE 6 (HDAC6) PROTECTS AGAINST VINCRISTINE-INDUCED PERIPHERNAL NEUROPATHIES AND INHIBITS TUMOR GROWTH

Lawrence Van Helleputte

(1,2) Van Helleputte L, (1,2) Kater M, (3) Cook D, (1,2) Haeck W, (1,2) Jaspers T, (1,2) Geens N, (4) Vanden Berghe P, (3) Geysemans C, (1,2) Robberecht W, (1,2,5) Van Damme P, (6) Cavaletti G, (7) Jarpe M and (1,2) Van Den Bosch L. (1) KU Leuven - University of Leuven, Department of Neurosciences, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), Leuven, Belgium; (2) VIB, Center for Brain & Disease Research, Laboratory of Neurobiology, Leuven, Belgium; (3) KU Leuven - University of Leuven, Clinical and Experimental Endocrinology, Leuven, Belgium; (4) KU Leuven - University of Leuven, Laboratory for Enteric Neuroscience, TARGID, Leuven, Belgium; (5) University Hospitals Leuven, Department of Neurology, Leuven, Belgium; (6) Experimental Neurology Unit and Milan Center for Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy; (7) Acetylon Pharmaceuticals Inc., Boston, MA, USA

P4_12 PERIPHERAL NEUROTOXICITY IN OXALIPLATIN RETREATMENT IN COLORECTAL CANCER PATIENTS

Roser Velasco Fargas

(1) Besora S, (2) Santos C, (1) Izquierdo C, (2) Martinez-Villacampa M, (1) Simó M, (1,3) Bruna J, (1,3) Velasco R. (1) Neuro-Oncology Unit, Hospital Universitari de Bellvitge-Institut Català d´Oncologia, L´Hospitalet, Barcelona, Spain. (2) Medical Oncology Department, Institut Català d´Oncologia, L´Hospitalet, Barcelona, Spain. (3) Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, and Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain

P4_13 SCHWANN CELL p75NTR EXPRESSION AND DIABETIC NEUROPATHY

Nadia Goncalves

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P4_14 ROLE OF L-PGDS IN SCIATIC NERVE REGENERATION AFTER INJURY

Maria Grazia Forese

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P4_15 LOCAL INFUSION OF A LOW DOSE OF CURCUMIN IMPROVES NERVE REGENERATION AND FUNCTIONAL RECOVERY IN RATS SUBMITTED TO SCIATIC NERVE CRUSH INJURY

Martial Caillaud

(1) Caillaud M, (1,2) Richard L, (1) Vignaud L, (1,2) Vallat Jm, (1) Desmouliere A, (1) Billet F. (1) EA 6309 - Myelin Maintenance & Peripheral Neuropathies, Faculties of Medicine and Pharmacy, University of Limoges, Limoges, France; (2) Department of Neurology, Reference Center for Rare Peripheral Neuropathies, University Hospital of Limoges, Limoges, France

P4_17 VOLUNTARY EXERCISE MODULATES MACROPHAGE POLARIZATION FOLLOWING SCIATIC NERVE INJURY AND IMPROVES FUNCTIONAL RECOVERY IN MICE

Megan Jack

Jack MM, Wright DE. The University of Kansas Medical Center, Kansas City, USA

P4_18 RESTORATION OF NEUROMUSCULAR FUCTION IN A MOUSE MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A BY DIFFERENTIATED HUMAN TONSIL-DERIVED MEESENCHYMAL STEM CELLS

Sung-Chul Jung

(1) Jung SC, (1) Park S, (1) Choi Y, (2) Kwak G, (2) Hong YB, (1) Jung N, (3) Chung KW, (2) Choi BO (1) Ewha Womans University, Seoul, Republic of Korea; (2) Sungkyunkwan University, Seoul, Korea; (3) Kongju National University, Gongju, Republic of Korea

P4_19 IN VITRO MORPHOLOGICAL STUDY OF BORTEZOMIB-INDUCED PERIPHERAL NEUROTOXICITY

Alessio Malacrida

(1) Rodriguez-Menendez V, (1) Ballarini E, (1,2) Malacrida A, (1) Ceresa C, (1,2) Semperboni S, (1) Meregalli C, (1), Cavaletti G, (1) Nicolini G. (1) School of Medicine and Surgery, Experimental Neurology Unit, University of Milano-Bicocca, Monza, Italy; (2) PhD program in Neuroscience, University of Milano-Bicocca, Monza, Italy

P4_20 TRPV1 ACTIVATION BY CAPSAICIN ENHANCES THE REGENERATION OF SENSORY NEURONS

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P4_21 FASCICULAR NERVE STIMULATION AND RECORDING USING A NOVEL DOUBLE-AISLE REGENERATIVE ELECTRODE

Jaume del Valle
(1,2) Del Valle J, (1) Delgado-Martínez I, (3) Righi M, (1,2)Santos D, (3) Cutrone A, (4) Bossi S, (3) D'Amico S, (3,5) Micera S, (1,2) Navarro X. (1) Institute of Neurosciences, Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra, Spain; (2) Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Bellaterra, Spain; (3) The Biorobotics Institute, Scuola Superiore Sant'Anna, Pontedera, Italy; (4) Robotics Laboratory, ENEA, Casaccia Research Center, Roma, Italy; (5) Bertarelli Chair in Translational NeuroEngineering, Center for Neuroprosthetics, and Institute of Bioengineering, School of Engineering, Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

P4_22 INTRAVENOUS IMMUNOGLOBULIN THERAPY FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN PEDIATRIC PATIENTS: AN OBSERVATIONAL STUDY

Alphonse Hubsch
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P4_23 MALIGNANCY IN GUILLAIN-BARRE SYNDROME: A TWELVE-YEAR SINGLE-CENTER STUDY

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P4_24 THE FRANCOPHONE ANTI-MAG COHORT: LESSONS LEARNED FROM THE ANALYSIS OF 202 PATIENTS

Jean-Philippe Camdessanche
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P4_25 DISRUPTION OF BLOOD-NERVE BARRIER AT ENTRAPMENT SITES RATHER THAN NERVE ENDINGS IS THE LIKELY CAUSE OF SURAL-SPARING PATTERN IN GUILLAIN-BARRE SYNDROME

Yong Jian Cheng
(1) Cheng YJ, (1) Teng A, (1) Goh EJH, (2) T. Umapathi. (1) Yong Loo Lin School of Medicine, National University of Singapore, Singapore; (2) Department of Neurology, National Neuroscience Institute, Singapore

P4_26 CILOSTAZOL MODULATES SEQUENTIAL EXPRESSION OF MATRIX METALLOPROTEINASES AND THEIR INTRINSIC INHIBITOR WITHIN PERIPHERAL NERVOUS TISSUE DURING EXPERIMENTAL AUTOIMMUNE NEURITIS

Toshiki Fujioka
Hagiwara W, Konno S, Kihara, Inoue M, Fujioka T. Toho University, Tokyo, Japan

P4_27 LIFESTYLE AND DIETARY HABITS AS PREDISPOSING FACTORS FOR THE ONSET AND PROGRESSION OF CIDP: A CASE-CONTROL STUDY FROM THE ITALIAN CIDP DATABASE

Pietro Emiliano Doneddu
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P4_28 MRI BIOMARKERS TO ASSESS PROXIMAL NERVE INJURY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

Alina Sprenger
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P4_29 THROMBOEMBOLIC EVENTS IN INFLAMMATORY NEUROPATHY PATIENTS ON IVIG

Aisling Carr
Spillane J, Englezou C, Sarri-Gonzales S, Rossor A, Lunn MP, Manji H, Reilly MM, Carr AS. MRC Centre for Neuromuscular Diseases, National Hospital for Neurology, Queen Square, London, UK

P4_30 CAN NK CELLS HELP DISCRIMINATE IVIG TREATMENT RESPONSE IN PATIENTS WITH CIDP?

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P4_31 THE FOREARM/UPPER ARM RATIOS OF CROSS-SECTIONAL AREA ADD THE DIAGNOSTIC VALUE IN AMYOTROPHIC LATERAL SCLEROSIS

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P4_32 HEREDITARY OR INFLAMMATORY CHILDHOOD NEUROPATHY – ELECTROPHYSIOLOGICAL ABNORMALITIES HELPFUL IN THE DIFFERENTIATION

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P4_33 ULTRA HIGH FREQUENCY ULTRASOUND (UHFUS) NERVE IMAGING IN CIDP PATIENTS

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P4_35 SUBCUTANEOUS IMMUNOGLOBULIN IN CIDP: A TWO-YEAR EXPERIENCE

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P4_36 Ca(2+)-DEPENDENT ANTI-GANGLIOSIDE ANTIBODY IN SERONEGATIVE GUILLAIN-BARRÉ SYNDROME

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P4_37 PARANODAL ANTIBODIES IN AUSTRIAN PATIENTS WITH ACUTE ONSET INFLAMMATORY NEUROPATHY

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P4_38 ACUTE-ONSET OF CIDP WITH IGG4 ANTI-NF155 ANTIBODIES RESISTANT TO CONVENTIONAL THERAPIES AND RESPONSIVE TO RITUXIMAB

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P4_39 TWO CASES OF IVIG RESPONSIVE INFANTILE ONSET AXONAL POLYNEUROPATHY

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P4_40 GLOBAL TRANSCRIPTOME ANALYSES REVEAL A KEY ROLE FOR MORC2 IN THE AXONAL METABOLISM

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P4_41 CMT1A PATIENTS GET OLD WORSE THAN HEALTHY PEOPLE

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P4_42 PXT3003, A FIXED COMBINATION OF BACLOFEN, NALTREXONE AND SORBITOL, FOR THE TREATMENT OF CHARCOT-MARIE-TOOTH DISEASE TYPE 1A (CMT1A): STATUS OF A MULTICENTER, DOUBLE-BLIND, PLACEBO- CONTROLLED, PIVOTAL PHASE III STUDY (PLEO-CMT)

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P4_43 WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS (ATTR-WT) AND PERIPHERAL NEUROPATHY

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P4_44 PILOT STUDY OF CLINICAL SEVERITY SCORE FOR HEREDITARY NEUROPATHY WIITH LIABILITY TO PRESSURE PALSIES

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P4_45 IDENTIFICATION OF COMMON MOLEUCLAR PLAYERS INVOLVED IN THE PROGNOSIS AND PATHOGENESIS OF AXONAL CMT SUBTYPES

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P4_46 NATURAL HISTORY STUDY IN HEREDITARY SENSORY NEUROPATHY TYPE 1 (HSN1): IMPROVING THE RESPONSIVENESS OF OUTCOME MEASURES

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P4_47 ABSENCE OF NEUROFILAMENT LIGHT CHAIN IN PATIENT-SPECIFIC MOTOR NEURONS IN AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE

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P4_48 MODELING THE PATHOGENESIS OF CHARCOT-MARIE-TOOTH DISEASE TYPE 1A USING PATIENT-SPECIFIC IPSCS

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P4_49 MITOCHONDRIAL DYSFUNCTION AND ABNORMAL CALCIUM HANDLING IN CELLULAR MODELS OF HEREDITARY SENSORY NEUROPATHY TYPE 1

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P4_50 A COMBINATION OF THREE REPURPOSED DRUGS (PXT3003) SYNERGISTICALLY INCREASES MYELINATION IN CO-CULTURES OF SCHWANN CELLS AND NEURONS DERIVED FROM CMT1A RATS

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P4_51 RATE OF PROGRESSION IN PEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

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P4_52 CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: INFLUENCE OF BODY MASS INDEX ON NERVE CONDUCTION STUDIES AND ON THE CHARCOT MARIE TOOTH EXAM SCORE

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P4_53 DIAGNOSTIC YIELD OF A 6,000 DISEASE-ASSOCIATED GENE FOCUSED EXOME IN CMT AND COMPLEX NEUROPATHY CASES: AN EXPLORATORY STUDY

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P4_54 BIOMARKERS OF SMALL FIBER NEUROPATHY IN AMYLOID NEUROPATHY

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P4_55 AEROBIC EXERCISE FOR SUBJECTS AFFECTED BY CHARCOT MARIE TOOTH (CMT) NEUROPATHY: RESULTS OF A MULTICENTER, PROSPECTIVE, RANDOMIZED, SINGLE BLIND, CONTROLLED CLINICAL TRIAL

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P4_56 DYSREGULATED LIPID METABOLISM IN THE ABSENCE OF PERIPHERAL MYELIN PROTEIN 22 (PMP22)

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P4_57 INVESTIGATION OF SELECTIVE HISTONE DEACETYLASE 6 INHIBITORS AS A TREATMENT FOR CHARCOT-MARIE- TOOTH DISEASE TYPE 1A USING A CO-CULTURE SYSTEM

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P4_58 THE COMBINATIONAL DRUG PXT3003 IMPROVES NEUROMUSCULAR FUNCTION IN AN ANIMAL MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A DISEASE

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P4_59 A GENE THERAPY APPROACH FOR TREATING CMT4C NEUROPATHY

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P4_60 A COMPLEX HOMOZYGOUS MUTATION IN ABHD12 RESPONSIBLE FOR PHARC SYNDROME DISCOVERED BY NGS

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P4_61 GAIT PATTERNS OF CHILDREN WITH CMT TO INFORM THE DESIGN OF 3D PRINTED ORTHOSES

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P4_62 DO ORTHOSES IMPROVE GAIT IN CHILDREN AND ADOLESCENTS WITH CHARCOT-MARIE-TOOTH?

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P4_63 A PATIENT WITH ATAXIA WITH OCULOMOTOR APRAXIA TYPE 1 AND SLOW CONDUCTION VELOCITIES

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P4_64 EMG PATTERNS IN FAMILIAL AMYLOIDOTIC POLINEUROPATHY (FAP) DUE TO TTR MUTATIONS

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P4_65 TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY IN POLAND- GENOTYPIC AND CLINICAL PRESENTATION

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P4_66 A NEW AUTOSOMAL RECESSIVE AMYELINATING CAUSE OF CHARCOT MARIE TOOTH DISEASE WITH CNS FEATURES AND RESPIRATORY DISTRESS

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P4_69 CHALLENGES IN NEUROLOGICAL PRACTICE IN LAO P.D.R

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RP Bunge Lecture

MOLECULAR ASPECTS OF THE FORMATION/MAINTENANCE OF THE NODE OF RANVIER

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Two Schwann cell-dependent mechanisms control the presence of Na^+ channels at the nodes of Ranvier: ***i.*** clustering of the nodal complex by glia-derived proteins and ***ii.*** restriction of nodal proteins within the nodal gap by the paranodal junctions. These mechanisms depend on specific cell adhesion molecules that mediate the contact between myelinating glia and their underlying axons at the forming nodes and the paranodal junction. During myelination, Na^+ channels initially clustered at heminodes that border each myelin segment. This process requires gliomedin, NrCAM and neurofascin 186 (NF186), three cell adhesion molecules (CAMs) that mediate the interaction between Schwann cell microvilli and the axon. Na^+ channels clustering activity of gliomedin is tightly regulated by two distinct and functionally opposing proteolytic events. While the clustering activity of gliomedin is enhanced by its shedding from the surface of Schwann cells by a furin protease, its activity is negatively regulated by bone morphogenetic protein 1/Tolloid-like (BMP1/TLD), and Tolloid-like 1 (Tll1) metalloproteinase. Cleavage by these enzymes restricts the activity of gliomedin to the nodal area and prevents the formation of ectopic clusters along axons that are devoid of myelin segments, as well as below the myelin internodes. Hence, proteolytic processing of gliomedin facilitates, yet limits, the clustering of Na^+ channels to specific sites along the axon in a timely manner. Furthermore, axon-glial contact mediated by gliomedin and NF186 at the nodes, not only plays a role in Na^+ channel clustering during development, but also contributes to the long-term maintenance of Na^+ channels at nodes of Ranvier. In addition to clustering by gliomedin, the distribution of Na^+ channels is restricted between two growing myelin segments by the flanking paranodal junction. At this site, axon-glia contact is mediated by a distinct set of cell adhesion molecules (i.e., Caspr, NF155 and contactin) that also delineate the underlying axonal and glial cytoskeleton. This paranodal junction-dependent restriction of Na^+ channels to the nodes is mediated by the spectrin-based paranodal axonal cytoskeleton.

AK Asbury Lecture

CLINICAL ASPECTS AND NEW ANIMAL MODELS OF AUTO-IMMUNITY TO NODAL COMPONENTS

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disorder of the peripheral nerves with clinical and immunological heterogeneity. Currently, the diagnosis of CIDP is based on clinical and electrophysiological criteria and does not take into consideration the presence of immune biomarkers. Several autoantibodies against proteins of the node of Ranvier in patients with CIDP have now been described. These antibodies define specific CIDP subtypes sometimes referred to as nodopathies and can have diagnostic and prognostic implications.

Anti-Contactin 1 (CNTN1) antibodies. We have described the presence of antibodies to CNTN1 in a small subset of patients with CIDP. These patients shared a phenotype and have poor response to IVIg. The anti-CNTN1 antibodies are predominantly IgG4. Pathological studies from skin and sural nerve biopsies of patients show morphological changes in the paranodes. Experimental data supporting the pathogenicity of anti-CNTN1 IgG4 antibodies include: A) demonstration *in vitro* that the antibodies disrupt the binding of the CNTN1–CASPR1 complex to neurofascin-155 (NF155); B) intraneural injections of antibodies progressively and specifically disrupt the paranodal axo-glial junction; and C) chronic infusion of antibodies induced clinical and electrophysiological worsening in animals with experimental autoimmune neuritis (EAN).

Anti-NF155 antibodies. Antibodies to neurofascins were first reported in patients with Guillain-Barré (GBS) and CIDP and subsequently, antibodies specific to the NF155 isoform were found in a small group (<3%) of patients with CIDP. Studies by us and confirmed by others have demonstrated that patients with CIDP and anti-NF155 antibodies have a distinct phenotype that often includes a low-frequency tremor and poor responses to IVIg. The autoantibodies are predominantly of the IgG4 subtype. The passive transfer of monoclonal anti-neurofascin antibodies (which recognize all neurofascin isoforms) to mice with EAN strongly exacerbated the severity of the pathology, but no studies have yet demonstrated that patient-derived anti-NF155 IgG4 antibodies are pathogenic. A pathogenic role of the antibodies is however supported by sural nerve biopsies from patients with CIDP and anti-NF155 antibodies that showed paranodal demyelination in the absence of inflammation, the loss of septate-like junctions and, the interposition of cellular processes between the paranodal loops and the axolemma. These alterations are reminiscent of those found in *Nfasc*-null mice suggesting that anti-NF155 antibodies may specifically disrupt the NF155–CNTN1–CASPR1 complex at the paranodes.

Antibodies to other nodal proteins. Recently *neurofascin-186 and neurofascin-140* were reported as the main targets of autoantibodies in five patients with IgG reactivity against the nodes of Ranvier; the antibodies were predominantly IgG4. These patients presented with clinical features distinct from those in patients with anti-NF155 IgG4 antibodies. Four of these patients had subacute onset of sensory ataxia without tremor. The presence of *anti-CASPR1 antibodies* has been reported in two patients with inflammatory neuropathies, one classified as CIDP, the other as GBS. Both patients had intense neuropathic pain. The skin biopsy from both patients showed paranodal disruption. Some patients whose sera show nodal or paranodal reactivity in teased nerve fiber preparations have antibodies against other nodal proteins, such as gliomedin or neuronal cell adhesion molecule (NrCAM).

Treatment of nodopathies. Corticosteroids are reported effective in approximately 40-60% of cases. Clinical remission has been noted following rituximab, and was associated with autoantibody depletion and neurophysiological improvement.
Conclusions. The clinical and immunological heterogeneity of CIDP is being unraveled with the description of specific autoantibodies and their association with disease phenotypes. For some of these autoantibodies, such as CNTN1 and NF155, we have shown their clinical value and association with treatment response, as well as a pathogenic role in these immune neuropathies that are now recognized as nodopathies. On-going research will determine if there are additional clinically valuable immune associations in other subgroups of CIDP patients.

JW Griffin Lecture

METABOLIC SUPPORT OF AXONS BY SCHWANN CELLS

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Axon degeneration is a form of programmed subcellular death that is a central, perhaps initiating event, in many neurological disorders. NAD metabolism plays a central role in this self-destructive process, which also requires the Toll-like receptor adaptor, SARM1, and MAP kinases, including DLK. The dismantling of damaged axons can be prevented by NAD biosynthetic enzymes. This was first observed in studies of the Wlds mutant mouse, with later work showing that the short-lived NMNAT2 isoform located in the axon helps block activation of this degeneration pathway. SARM1 is the central executioner of the axonal degeneration pathway and its activation culminates in depletion of axonal NAD^+, yet the identity of the underlying NAD^+- depleting enzyme(s) was unknown. We have now discovered that the SARM1-TIR domain itself, which is commonly appreciated as a scaffolding domain, has intrinsic NADase activity—cleaving NAD^+ into ADP-ribose (ADPR), cyclic ADPR, and nicotinamide. Mutation analysis of SRM1 showed that its NADase activity is necessary for axon degeneration after injury, suggesting that SARM1 represents a novel therapeutic target for peripheral neuropathy and other neurodegenerative conditions.

PJ Dyck Lecture

MECHANOTRANSDUCTION AND PAIN

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The skin is equipped with specialized mechanoreceptors that allow the perception of the slightest brush. Indeed some mechanoreceptors can detect even nanometer-scale movements. Movement is transformed into electrical signals via the gating of mechanically-activated ion channels at sensory endings in the skin. The sensitivity of PIEZO mechanically-gated ion channels are controlled by stomatin-like protein-3 (STOML3), which is required for normal mechanoreceptor function. Under pathophysiological conditions following nerve injury or diabetic neuropathy the slightest touch can produce pain. It is at present unclear whether peripheral changes in sensory mechanotransduction may underlie hypersensitivity associated with neuropathic pain. Here we have examined the role of the STOML3 modulation of PIEZO2 channels in mechanoreceptors and nociceptors to under pathophysiological conditions. We recently developed small molecules that act as inhibitors of STOML3 function. Peripheral application of STOML3 inhibitors can alleviate hypersensitivity in models of neuropathic pain. Our data strongly suggest that tactile evoked pain in models of peripheral neuropathy may be at least partly driven by sensitization of sensory mechanotransduction driven by STOML3.

PK Thomas Lecture

THE CONTROL OF WALLERIAN DEGENERATION AND ITS RELEVANCE TO PERIPHERAL NEUROPATHY

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Axons are lost early in many neurodegenerative disorders of peripheral and central nervous system. The degeneration of transected axons (Wallerian degeneration) can be slowed tenfold by overexpression of a variety of NAD-synthesizing enzymes, such as isoforms of NMNAT or the related mutant fusion protein, WLD^S. Wallerian degeneration is also delayed by deletion of TLR adapter protein SARM1, a protein recently reported to promote NAD degradation. It is important to understand fully the mechanism of Wallerian degeneration because related mechanisms contribute to axon loss in a number of disease models, including models of peripheral neuropathies, Parkinson's disease, multiple sclerosis and glaucoma. New data also suggest a role in hereditary spastic paraplegia.
While depletion of NAD is an attractive hypothesis for the mechanism of Wallerian degeneration, especially as NAD can be increased by dietary methods, it cannot explain a number of key observations. FK866, an inhibitor of NAMPT, blocks the NAD salvage pathway and strongly depletes NAD, including within axons. However, instead of killing axons as the NAD hypothesis would predict, it does precisely the opposite: it phenocopies the protective effect of WLD^S. Moreover, ectopic expression of the bacterial enzyme NMN deamidase, a protein absent in mammals, protects injured axons both in transgenic mice and in primary neuronal cultures, but it has no effect on NAD levels either under basal conditions or in degenerating nerves. These observations fit better with a proposed toxic role for the NAD synthesis intermediate NMN, a model that can also explain the protective effect of WLD^S. A full understanding of the pathway should identify a number of points where intervention could be a treatment for multiple axonopathies.

Plenary Lecture

NEURO-EPIDEMIOLOGY AND ITS RELEVANCE TO PHERIPHERAL NEUROPATHY

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As with any medical discipline, expansoin of knowledge about the fundamental science behing a disorder of the human nervous system comes part and parcel with a change in our understanding of the epidemiology of any given disorder or groups of disorders. Recent advances in our fundamental understanding of inflammatory neuropathies of the peripheral nervous system have been accompanied by drastic changes in our understanding of the neuroepidemiology of these disorders – the specific populationss affected by peripheral neuropathies, as well as the varying importance / contributions of select peripheral neuropathies to the overall burden of peripheral nervous system (PNS) disease, and how this shift in epidemiological understanding influences the clinical approach to diagnosis and management of patients with PNS disease. The past few decades have witnessed a paradigm shift in many aspects of PNS disease diagnosis and treatment; from the association of human immunodeficiency virus (HIV)-associated neuropathies; to the increassing recognition of hereditary / familial peripheral neuropathies; to the increased recognition of specific neuropathies such as multifocal motor neuropathy with conduction block. In addition, timely events such as the recent, and increasingly irrefutalbe evidence for a link between Zika virus and a Guillain-Barré syndrome, and the rather unexpected resurgence of peripheral neuropathies due to previously ‘exotic’ etiologies such as lepromatous neuropathy require prompt clinical attention. This plenary session aims to describe the evolving neuroepidemiology of peripheral nervous system disorders, and how these changes may influnece the clinical approach to the diagnosis, prognostication, and treatment of otherwise ‘unusual’ periphal nerve diseases.

PNS Meeting Abstracts

LECITHIN THERAPY AMELIORATES DISEASE PROGRESSION IN A RAT MODEL OF CHARCOT MARIE TOOTH DISEASE 1A

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Charcot–Marie–Tooth disease is the most common inherited neuropathy and a duplication of the peripheral myelin protein 22 gene (PMP22) causes the most frequent sub-form Charcot–Marie–Tooth 1A (CMT1A). In contrary to the notion that CMT1A manifests in the second decade of life, moderate walking disability and electrophysiological abnormalities are usually already present during childhood. The early onset and developmental nature of the disease is also supported by findings derived from a *Pmp22* transgenic rat model for CMT1A (CMT rat), which displays a reduced number of myelinated fibers per peripheral nerve already early postnatally and never reaches a wildtype level throughout development. In line, CMT rat Schwann cells show a strongly impaired lipid biogenesis required for myelination as assessed by RNA expression and lipid profiling of peripheral nerve transcriptomes and myelin composition, respectively. Importantly, *Pmp22* overexpressing Schwann cells also reflect an impaired myelination competence *in vitro*, when co-cultured with dorsal root ganglia neurons. A remarkable improvement of Schwann cell myelination upon supplementation with phosphatidylcholine *in vitro* has led to the hypothesis that exogenous supplementation with lipids *in vivo* may improve disease progression. Indeed, we observed improved disease progression on the histological, electrophysiological and behavioral levels in CMT rats which were fed with a chow enriched in lecithin from P2 to adulthood. Moreover, disease amelioration is also visible after late long-term (P21-P112) and early short-term treatment (P2 to P21), but the effect is fading after treatment cessation. Therefore, continuously supplying patients with exogenous lipids may be considered as a promising therapeutic approach for CMT1A disease.

AN *IN VIVO* AND *IN VITRO* NEUROPHYSIOLOGICAL APPROACH TO ACUTE AND CHRONIC OXALIPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

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Oxaliplatin chemotherapy for colorectal cancer is seriously limited by neurotoxic side effects which are not fully understood. Oxaliplatin-induced peripheral neurotoxicity (OIPN) comprises an acute syndrome and a chronic sensory neuropathy. The acute symptoms, notably cold hyperalgesia, have been attributed to transient ion channel dysfunction, and the worse they are the more severe the chronic neuropathy that ensues. We designed a combined *in vitro* and *in vivo* project, using neurophysiology to better understand the pathogenesis of OIPN. In the *in vitro* study, differentiated F11 cells (rat DRG neurons x mouse neuroblastoma N18TG-2 cell line) were incubated for 24 and 48 hours in 7.5 □M oxaliplatin, and their electrophysiological properties studied by patch-clamp. The treated F11 cells showed relatively depolarized resting membrane potentials, significantly decreased firing frequencies, and increased sodium current densities. Moreover, a decrease in ERG (ether-à-go-go-related gene) potassium current was also evident. In the *in vivo* study, we applied Nerve Excitability Testing (NET) to a Wistar rat model of OIPN. To investigate the acute syndrome, we compared behavioural and neurophysiological data of 2 animal cohorts (controls and OIPN rats, n=9 each) before and after Oxaliplatin administration (5mg/Kg, iv). Twenty-four hours after the injection we observed differences between the 2 groups in behaviour (cold plate test, P=0.008) and in superxcitability of motor axons (P=0.002). To investigate the chronic neuropathy, we compare a control group (n=10) with a treated group (n=10, oxaliplatin 3 mg/Kg twice weekly x 4 weeks, iv). Both groups are studied with behavioural, neurophysiological (sensory and motor nerve conduction studies, NET), and pathological (caudal and sciatic nerve, skin biopsy, DRGs) methods. Data are collected at baseline, end of treatment and 6 weeks after treatment; to obtain a full NET profile of all significant changes. In this highly translational approach to OIPN, the *in vivo* NET changes in the acute and chronic rat models can be matched on the one hand to findings from *in vitro* experiments, and on the other to clinical data, since NET is also easily applied in humans.

EPIDEMIOLOGY OF GUILLAIN-BARRÉ SYNDROME IN DENMARK – THE INTERNATIONAL GBS OUTCOME STUDY IN A POPULATION BASED PERSPECTIVE

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The International GBS Outcome Study (IGOS) is a prospective observational international study aiming to identify clinical and biological determinants of disease progression and outcome in a large cohort of GBS patients. Demographic and clinical characteristics of the first 1000 included patients will be analysed and presented. However, within IGOS there is no population based control group, and therefore it is important to assess the generalizability of these results. In Denmark there is a unique situation to conduct epidemiological studies facilitated by The Danish Civil Registration and The Danish National Hospital Registry (DNHR). This enables us to identify all GBS patients in Denmark in a given period. From the same period as the IGOS 1000 cohort was included we have identified all GBS patients admitted to or seen in outpatient's clinics of hospitals in Denmark (September 1st 2012 to December 31st 2015). Records from the population based Danish cohort will be reviewed for demographic and clinical data and compared to the patients included in IGOS from Denmark, as well as with the IGOS 1000 Europe/America cohort. During this period 93 patients from Denmark have been included in IGOS. The Danish group is comparable to the Europe/America group not counting the Danish patients (n=640) of the IGOS1000 cohort in regard to sex and age at entry, GBS disability score at nadir, and percentage of patients needing mechanical ventilation. In the Danish IGOS group 57% are males, the median age is 58(39-67) years, the mean(SD) GBS disability score at nadir 3.6 (1.0), and 18 % of the Danish group needed mechanical ventilation. In the Europe/America group 59% are males, the median age is 54(37-66), mean(SD) GBS disability score at nadir 3.5(1.0) and 17 % of the group needed mechanical ventilation. At the meeting we will compare and present data from the Danish population based cohort as well as epidemiological data.

ITG2A-EXPRESSING SCHWANN CELLS UPREGULATE A MACROPHAGE RECRUITMENT FACTOR PERIOSTIN DURING SPONTANEOUS AUTOIMMUNE PERIPHERAL NEUROPATHY.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a common autoimmune disease of the peripheral nervous system (PNS) that causes sensorimotor impairment. Mice with a dominant Autoimmune Regulator gene (Aire) G228W mutation on the non-obese diabetic (NOD) background (NOD.Aire$^{GW/+}$ mice) develop spontaneous autoimmune peripheral polyneuropathy (SAPP) resembling CIDP. In SAPP, demyelination is caused primarily by Th1 T cells; however, the contributions of nerve-resident cells such as Schwann cells are poorly understood. We identified a population of non-hematopoietic, integrin alpha 2+ (Itga2+) cells in the PNS that increases in frequency and number during SAPP. These Itga2+ cells coexpress numerous Schwann cell markers including Sox10, P75, S100b, myelin protein zero, and peripheral myelin protein 22, suggesting that Itga2+ cells are Schwann cell-like. Additionally, during SAPP, these Itga2+ cells upregulate the extracellular matrix protein periostin (Postn), which has recently been shown to promote macrophage recruitment and activation in inflammatory disease and cancer. Our data indicate that macrophages are pathogenic during SAPP. Therefore, we hypothesized that Itg2a+ cells promote macrophage recruitment during SAPP via Postn production. To test this hypothesis, we performed *in vitro* chemotaxis assays. Conditioned media from NOD.Aire$^{GW/+}$ nerve promoted significantly more macrophage chemotaxis than conditioned media from Postn$^{-/-}$ nerve. Furthermore, Postn recombinant protein was sufficient to induce macrophage chemotaxis *in vitro*. Our findings show that Itg2a+ Schwann cell-like cells mediate macrophage chemotaxis by upregulating Postn during SAPP and suggests Postn as a novel target for the treatment of CIDP.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) TREATMENT-RELATED FLUCTUATIONS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP) PATIENTS USING DAILY GRIP STRENGTH MEASUREMENTS (GRIPPER): STUDY DESIGN AND PROGRESS UPDATE

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Although IVIg efficacy for the treatment of CIDP has been demonstrated in randomized controlled trials, the optimal treatment approach for patients on chronic therapy is unknown. Herein we update progress on the investigator-initiated, multi-center "GRIPPER" study that prospectively evaluates "wear-off" or other IVIg treatment-related fluctuations in patents with CIDP. The primary outcome measure is Jamar grip strength (GS), performed daily for 6 months. Home nursing visits also capture Rasch-built Overall Disability Score (R-ODS), Timed Up and Go Test (TUGs), Overall Neuropathy Limitations Scale (ONLS), Modified Fatigue Severity Scale (mFSS), and Visual Analog Pain Severity Scale (VAS) weekly for 6 months. The QOL Short Form Physical Component Summary (SF-36v2®) is collected at baseline, week 12, and week 24. Serum IgG levels are collected at 3 time-points surrounding IVIg infusions (peak, trough, and mid-cycle). Total recruitment is anticipated to be 30 subjects. Upon study completion "wear-off" frequency will be analyzed by assessing the proportion of subjects with any given degree of GS and RODS intracycle fluctuation and the proportion of cycles in which GS and R-ODS fluctuation occurs. To determine the extent of "wear-off" the degree of difference between maximum and minimum GS, R-ODS, TUGs, ONLS, and VAS scores will be analyzed. Currently 22 subjects from 4 different sites have been enrolled (7 sites eligible for enrollment). This interim study report will provide preliminary representative data, demonstrating IVIg "wear-off" effects on GS and other outcome measures. By better understanding the frequency and extent of IVIG treatment-related fluctuations we expect that these results will help facilitate development of CIDP treatment optimization strategies. We also expect that this information will be important in forming hypotheses to be tested in future studies (for example, comparing different dosage intervals, optimal IVIg taper guidelines, or assessing the long-term outcome of short-term cycle to cycle clinical fluctuations).

EVALUATION OF MOLECULAR INVERSION PROBE VERSUS TruSeq® CUSTOM-NEXT GENERATION SEQUENCING METHODS TO IDENTIFY GENETIC VARIATIONS IN PAINFUL NEUROPATHIES- THE PROPANE STUDY

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Neuropathic pain is a frequent feature of peripheral neuropathy causing a significant impact on patients' quality of life and health care costs. Resolving the genetic architecture of painful neuropathy will lead to better disease management strategies, risk stratification, and counselling. Therefore, we aim to develop a reliable technique to rapidly and accurately re-sequence multiple genes in a large cohort of painful neuropathy patients at low cost. Whole exome sequencing of thousands of samples remains expensive for clinical use. Several targeted enrichment approaches are currently available to selectively enrich for genomic regions of interest. In this study, we compared the sensitivity, specificity, targeting efficiency, reproducibility of performance and cost effectiveness of TruSeq® Custom Amplicon-Next generation sequencing (TSCA-NGS) and Molecular Inversion Probes- Next generation sequencing (MIPs-NGS) methods. For both methods, we constructed a targeted enrichment kit to capture the coding and exon-flanking intron sequences of nine sodium channel genes (*SCN3A, SCN8A-SCN11A*, and *SCN1B-4B*) expressed in nociceptive neurons. Probes were designed for the two methods using their respective informatics pipelines. In total, 180 patients with diabetic and idiopathic neuropathy were tested by both methods. Among the 180 patients, 70 patients were tested previously by Sanger sequencing for *SCN9A-SCN11A*. Approximately 39kb was captured and sequenced. 95% of the targeted regions showed an average coverage of ≥20x in TSCA-NGS, and 96% in MIPs-NGS. We managed to identify 12 potential pathogenic mutations and 1294 polymorphism variants by MIPs-NGS and TSCA-NGS. Moreover, we observed a perfect agreement (100%) between Sanger sequencing data and those obtained using MIPs-NGS and TSCA-NGS. Both NGS approaches showed user-*friendly software to design probes and* exhibited a similar on-target efficiency. Although the overall coverage per region varied across different DNA samples, it was sufficient to detect any variant in these regions. MIPs-NGS has more versatile assay design, demonstrated a high degree of flexibility with probes re-placement and >10x cheaper than TSCA-NGS. MIPs-NGS is a reliable, flexible, and inexpensive method to detect genetic variations in thousands of patients. In our centers, this technology is currently implemented as a routine diagnostic tool for screening of sodium channel genes in painful neuropathy patients.

ACUTE DEMYELINATING POLYNEUROPATHY RESEMBLING GUILLAIN-BARRE SYNDROME IN A

PATIENT TAKING THE SLIMMING PRODUCT PURA ALEGRÍA ®

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Most acute demyelinating polyneuropathies have an immune-mediated pathogenesis and are included within the Guillain-Barré syndrome spectrum. Occasionally, other mechanisms such as metabolic, infectious or toxic may lead to GBS-like presentations. Thermatrim® and Pura Alegria® are different brands of the same illegal slimming product that is sold through online vendors and in which the exact composition is unknown. Here we present a patient with an acute demyelinating polyneuropathy secondary to the intake of the slimming product "Pura Alegría".

A 50 year-old woman with no remarkable medical history reported 7 days history of distal numbness in her feet that progressed in one week to her knees and her left hand. She had had an upper respiratory tract infection ten days prior to these symptoms. The neurological examination showed absent distal vibratory and arthrokinetic sensations and arreflexia in lower limbs, decreased vibratory sensation in her hands and a ataxic gate. The lumbar puncture showed 0.89 g/l of proteins with no cells. The EMG fulfilled diagnostic criteria for acquired demyelination. Intravenous immunoglobulin therapy was started but the symptoms kept worsening and corticosteroids were started. The patient mentioned then the slimming product. A brain MRI showed diffuse leukoencephalopathy that was asymptomatic. Steroids and the Pura Alegria slimming products were withdrawn and the patient recovered completely after one year of follow-up.

"Pura Alegría", "Thermatrim" and "Thermatrim plus" are slimming products that were forbidden in Spain after several cases of acute leukoencephalopathy and acute polyneuropathy. Exact composition is unknown although the Spanish Drug Agency detected the pesticide malonoben, a tyrosin kinase inhibitor, among the components. Since 2014 nine cases of Pura Alegria/Thermatrim neurological toxicity, including leukoencephalopathy and polyneuropathy have been described. All cases had good outcomes after treatment withdrawal, although recovery is slow and may be incomplete.

Our case highlights the need to carefully consider drug toxicity, including dietary supplements, in the differential diagnosis of GBS specially when evolution does not follow typical patterns.

IMPAIRED MOTOR AXON EXCITABILITY IN A MOUSE MODEL OF CMT1A

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Charcot-Marie-Tooth neuropathy type 1A (CMT1A) resulting from peripheral myelin protein 22 KDa (PMP22) overexpression is the most common hereditary motor and sensory neuropathy in humans. The transgenic PMP22 (PMP22tg) mouse line C61 carrying 4 copies of the human PMP22 gene, has a slowly progressing neuropathy phenotypically like CMT1A with thin and abnormally thick myelin profiles and supernumerary Schwann cells. In addition, PMP22tg nerves showed activated macrophages leading to axon-myelin compartment disruption and maldistribution of K+ channels (Kohl B et al, Am J Pathol. 2010; 176: 1390). The aim of the present study was to investigate the motor axon excitability in PMP22tg versus WT littermates. Multiple measures of motor axon excitability under anesthesia were carried out by stimulation of the tibial nerve at ankle and “threshold-tracking” the plantar compound muscle action potential (CMAP). At age 3 months, when the post-developmental maturation was nearly complete in the WT, the PMP22tg CMAP showed an increase in latency by 29%. The CMAP amplitude was decreased by 36%, although the mean motor unit size (MScan method) appeared unchanged indicating a lack of collateral sprouting. Furthermore, PMP22tg showed abnormalities in both passive cable properties and voltage dependent parameters. At age 6 month, the CMAP latency of PMP22tg was increased by 70% as compared to WT. In contrast to this marked conduction slowing along the tibial nerve from 3 to 6 months of age, the progression of excitability changes localized at ankle appeared modest. Nevertheless, when pooling data from 3 to 6 months, the increase in PMP22tg latency was correlated (Spearman $P<0.05$) with an increase in accommodation half-time during depolarizing electrotonus (+40% of threshold) from 29 to 35 ms and a reduction of the late subexcitable period of the recovery cycle from 16 to 9% of threshold, both changes consistent with a redistribution of K+ currents consistent with the maldistribution of K+ channels. Our data suggest that in the PMP22tg CMT1A model, a functional, thus potentially reversible abnormality in K+ channel distribution, accumulates along the nerve and aggravates the conduction impairment due to impaired myelin formation and maintenance.

LYSOPHOSPHATIDYLCHOLINE - INDUCED ACUTE DEMYELINATION AGGRAVATES MOTOR AXON DYSFUNCTION IN A MOUSE MODEL OF CMT1B

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Mice heterozygously deficient of myelin protein P_0 gene (P_0+/-) show a mild progressive dysmyelinating neuropathy, with conduction slowing and impaired excitability, phenotypically similar with Charcot-Marie-Tooth Disease type 1B (CMT1B). We found that in P_0+/- the accumulating myelin abnormalities were paralleled by progressive changes in voltage-dependent motor axon function resulting in neurotoxic membrane depolarization (Rosberg MR, et. al. Neurobiol Dis. 2016 93:201). The aim of this study was to investigate the relationship between demyelination and motor axon function in P_0+/-. Demyelination of the right sciatic nerve by topic lysophosphatidylcholine (LPC) application was carried out in P_0+/- and wild-type (WT) mice, in 1 year (mature) and 2 years (aged) groups. Multiple measures of motor axon excitability under anesthesia were carried out by stimulation of the tibial nerve at ankle (distal to LPC demyelination) and "threshold-tracking" the plantar CMAP responses. Live imaging studies by Cellvizio (Mauna Kea Technologies, Paris, France) confocal laser endomicroscopy were carried out in transgenic mice expressing the fluorescent reporter YFP in peripheral nerve axons under the Thy1 promoter. In mature WT the sciatic morphological and electrophysiological demyelinating features following LPC could be readily observed at 2 hours but disappeared by 2 weeks. No morphological changes could be observed at the tibial level. Consistently, no conduction or excitability changes could be observed at the right tibial neve level as compared to the left tibial nerve in WT. In contrast, in P_0+/- the motor axon function was impaired at the tibial nerve level at 2 weeks after sciatic LPC demyelination. In mature P_0+/-, although the CMAP amplitude appeared preserved, the distal motor latency was prolonged whereas the excitability measures showed reduced deviations during threshold electrotonus and increased refractoriness at the expense of superexcitability of the recovery cycle, both consistent with membrane depolarization. Furthermore, in aged P_0+/- the delayed tibial conduction was associated with a drop in CMAP amplitude and a prolongation of the strength-duration time constant. Taken together these data suggest that focal demyelination aggravates membrane dysfunction along the entire motor axon in P_0+/- providing a novel experimental model to explore the link between demyelination and axonal membrane dysfunction in CMT1B.

INFLUENCE OF BASELINE NEUROLOGIC SEVERITY ON DISEASE PROGRESSION AND THE ASSOCIATED DISEASE-MODIFYING EFFECTS OF TAFAMIDIS IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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A number of factors can influence disease progression in transthyretin familial amyloid polyneuropathy (TTR-FAP), a rare, fatal, hereditary amyloidosis. This analysis evaluated the specific role of baseline neurologic severity on neurologic disease progression in TTR-FAP. A predictive model was created based on longitudinal data from Val30Met patients who participated in the tafamidis (a selective TTR stabilizer) clinical development program. Data from the intent-to-treat population of the double-blind, placebo-controlled registration study (tafamidis group, n=64; placebo group n=61) and its two consecutive open-label extension studies in which all patients received tafamidis were used. The second extension study is ongoing, but a formal, prospectively-planned interim analysis was conducted with the cut-off date of December 31, 2014. This analysis focused on the first 12 months of treatment for the overall study cohort analyzed. The Neuropathy Impairment Score–Lower Limbs (NIS-LL) was used to assess neurologic functioning at baseline and at subsequent study visits. A linear mixed-effects model for repeated-measures (MMRM) analysis, with baseline NIS-LL, treatment, and their interactions with time as fixed effects, was used, and the slope and intercept for each patient were included as random effects. Patients were primarily Caucasian with early-stage neurologic disease (baseline NIS-LL mean [standard deviation]: tafamidis, 8.4 [11.4]; placebo, 11.4 [13.5]). Across both groups, disease progression increased with increasing levels of baseline severity (NIS-LL) ($p<0.0001$). However, the predicted magnitude of change from baseline to Month 12 for tafamidis was consistently less than that for placebo across a range of observed baseline NIS-LL values, suggesting a disease-modifying effect of tafamidis. Similar findings were observed for the NIS-LL muscle weakness subscale. This MMRM analysis in patients with Val30Met TTR-FAP demonstrates that disease progression strongly depends on baseline neurologic impairment and highlights the disease-modifying effect of tafamidis across a range of baseline levels of neurologic severity. ClinicalTrials.gov identifiers: NCT00409175, NCT00791492, NCT00925002.

ERAMUS GUILLAIN-BARRÉ SYNDROME RESPIRATORY INSUFFICIENCY SCORE IN JAPANESE PATIENTS

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Guillain-Barré syndrome (GBS) is a potential life threatening neurological disorder and respiratory insufficiency is one of the critical complications. Eramus GBS respiratory insufficiency score (EGRIS) is a method for predicting the chance of respiratory insufficiency in GBS. However, clinical characteristics and courses can vary for subtypes of GBS, whose occurrences differ for each region: acute inflammatory demyelinating polyneuropathy (AIDP) is very common in European countries, whereas acute motor axonal neuropathy (AMAN) is frequently seen in Asian countries. The aim of this study is to investigate the usefulness of EGRIS in Japan, where AMAN is more common than in the

Netherlands. Clinical and electrophysiological profiles of consecutive GBS cases, who visited our hospital within 28 days after symptoms onset between 1998 and 2015, were reviewed. Of the 150 GBS patients, 37 % were classified as AIDP and 20% as AMAN according to the electrodiagnosis criteria by Ho and colleagues. Higher EGRIS scores correspond to higher risk of respiratory insufficiency in total of the GBS patients, as well as in AIDP patients. However, in patients with AMAN, EGRIS scores did not always match the chances of respiratory insufficiency: up to 17% of the patients with low risk of EGRIS showed respiratory failure, whereas only 25% of the patients with high risk of EGRIS needs intubation/mechanical ventilation. In AMAN, associations with mechanical ventilation were seen for rapid progression (shorter duration between onset and hospital admission), more decreased vital capacity, and more frequent autonomic involvement. EGRIS is useful also for Japanese GBS patients. However, for AMAN patients, it should be used with discretion. Another score to predict respiratory insufficiency might be required in Asian countries.

A QUALITY IMPROVEMENT STRATEGY: ULNAR NERVE CONDUCTION STUDY OF THE FIRST DORSAL INTEROSSEOUS MUSCLE

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In patients with suspected ulnar neuropathy, nerve conduction studies (NCS) are commonly requested to help with diagnosis and localization. However, routine NCS are often normal or not localizing. Ulnar NCS recording from the first dorsal interosseous muscle (NCS-FDI) is thought to increase the diagnostic yield of electrodiagnostic testing, although not commonly considered. We developed a quality improvement strategy to routinely perform ulnar NCS recording from the abductor digiti minimi muscle (NCS-ADM) as well as ulnar NCS-FDI in all patients referred for suspected ulnar neuropathy. We utilized the DMAIC (Define, Measure, Analyze, Improve, Control) model of process improvement to define our problem and create a map of the current process for ulnar neuropathy diagnosis in our Electromyography laboratory. We determined baseline performance via review of the most recent 100 patients referred to our lab for a suspected ulnar neuropathy. Of the 100 patients reviewed, 38 patients demonstrated no electrodiagnostic evidence of an ulnar neuropathy. Ulnar NCS-FDI was not performed in any of these patients. In the 62 patients with ulnar neuropathy, two had a purely sensory neuropathy and one a dorsal cutaneous ulnar neuropathy. The 59 remaining patients had abnormal NCS-ADM. The ulnar neuropathy was localizable to the elbow in 20 (34%) of these patients and not localizable in the rest. Having defined the quality gap and measured baseline performance, the results of this analysis were used to develop targeted interventions intended to improve the performance of ulnar NCS-FDI. Data will then be remeasured and presented, specifically addressing the degree of improvement in the diagnostic yield of electrodiagnostic testing for ulnar neuropathy via routine performance of NCS-FDI.

DISTAL SENSORIMOTOR POLYNEUROPATHY FOLLOWING 13 YEARS OF TYPE 2 DIABETES ASSESSED BY THE MICHIGAN NEUROPATHY SCREENING INSTRUMENT QUESTIONNAIRE. A PROSPECTIVE STUDY, THE ADDITION DENMARK STUDY

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Distal sensorimotor polyneuropathy (DPN) is the most common complication of diabetes and risk factors beyond hyperglycemia have proven important particularly in type 2 diabetes (T2DM). Only few prospective studies from early-stage T2DM exist. We aimed to study the development of DPN during the first 13 years after a screening-based diagnosis of T2DM. From the ADDITION-Denmark study 1445 participants were eligible for this study. DPN was assessed by the Michigan Neuropathy Screening Instrument questionnaire (MNSI) at four time-points during follow-up. DPN was defined by a MNSI score ≥ 4. 189 participants (13%) were positive in MNSI at baseline and thus excluded from this study. By Kaplan-Meier plot we evaluated the cumulative incidence of DPN and in Cox proportional hazard models we calculated hazard ratios (HR) for the intervention groups in the ADDITION trial and for various covariates proposed to influence the development of DPN. Models were adjusted in steps for intervention group, age, sex, baseline MNSI, lipid-lowering and anti-hypertensive treatment. This study cohort consists of 1256 participants (59% men) with a median age of 60.8 years (p25;p75: 55.6;65.6) and median baseline HbA1c of 6.3 (p25;p75: 6.0;6.9). A cumulative incidence of 10% was seen during 13 years of diabetes. There was no statistically significant difference in HR between the intervention groups or by sex but a significantly higher HR of 1.03 (95%CI: 1.00;1.07) was seen for age (per year). The highest HR was found for a history of cardiovascular disease (myocardial infarction or stroke) up to ten years prior to the diabetes diagnosis with a HR of 3.04 (1.38;6.68). Weight, waist circumference, body-mass index and methylglyoxal (log^2 transformed) showed modest but statistically significant associations with incident DPN with standardized HRs of 1.35 (95%CI: 1.11;1.63), 1.35 (95%CI:

1.08;1.67), 1.39 (95%CI: 1.14;1.69) and 1.44 (95%CI: 1.12;1.86) respectively. This study demonstrates a fairly low cumulative incidence of DPN in people with screen-detected T2DM and provides evidence that macrovascular disease, obesity and oxidative stress are important risk factors for DPN even at the earliest stages of T2DM.

CHARCOT MARIE TOOTH DISEASE ASSOCIATED WITH AGENESIS OF THE CORPUS CALLOSUM: A HETEROGENEOUS ENTITY?

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Andermann syndrome, also known as agenesis of the corpus callosum and peripheral neuropathy (ACCPN), is an autosomal recessive disorder with a broad spectrum of mild to severe neuromuscular and psychiatric consequences. The gene variants causing disease were first identified in French-Canadian families. In the present study, we intended to phenotype and genotype a series of non-French-Canadian familial cases presenting with Charcot Marie Tooth disorder associated with agenesis/dysgenesis of the corpus callosum. For this purpose, seven families, 5 of consanguineous marriage, were studied. Patients were clinically and para-clinically investigated using MRI and electrophysiology (MNCVs). For some, a sural nerve biopsy was taken. Microsatellite markers around the ACCPN locus were used in two large families; followed by Sanger sequencing of all the exons and intron-exons boundaries of the gene, in one patient from each of the 7 families. The age at onset of the disease was at birth in the patients from the largest consanguineous family (3 affected individuals). The biopsy from one patient showed a severe demyelinating neuropathy with many hypomyelinated fibres and mostly secondary axonal changes. These finding were compatible with electrophsiological data where the MNCVs are of demyelinating range. Dysgenesis of the corpus callosum in one patient and Agenesis in another sib were revealed by MRI. We identified one homozygous truncating mutation in this family. Interestingly, no causative variant was found in a patient from another family and showing homozygous haplotype. Two different heterozygous variants were identified at one hit in two patients from two non-consanguineous families. Genetic investigations will be continued to identify the possible second hit. In the 4 remaining families, no variant was found. The negative family cases will be subjected to NGS. At this stage, it is tempting to speculate on the genetic heterogeneity of ACCPN in our series.

OCCURRENCE OF DIABETIC FOOT BY NCS-SEVERITY OF DIABETIC NEUROPATHY: A 5-YEAR PROSPECTIVE OBSERVATION

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In 2007 we introduced a staging system of severity of diabetic polyneuropathy (DPN) by nerve conduction study (NCS) of the lower limb: sensory NCS of the sural nerve and motor NCS of the tibial nerve. The system consists of five stages; NCS-0 (normal): no abnormalities, NCS-1 (mildly abnormal): presence of delay of MCV, SCV, minimal F-wave latency, or positive a-wave, NCS-2 (moderately abnormal): decrease in sural SNAP less than 5uV, NCS-3 (severely abnormal): decrease in plantar muscle-CMAP to 2-5mV, NCS-4 (ultimately abnormal): plantar muscle-CMAP lost or less than 2mV with trace of sural-SNAP. To examine validity of the system, we conducted 5-year prospective observation on development of diabetic foot (DF) by the NCS staging system. In addition, occurrence of ischemic heart disease (IHD) and stroke (IS), and death of neuro-vascular events were also counted. 1n 2007-09, we carried out NCS in 308 diabetics, and categorized them by the NCS staging system: 6% was NCS-0, 38% was NCS-1, another 38% was NCS-2, 10% was NCS3, and 7% was NCS-4. We then followed them and prospectively counted the occurrence of DF, IHD and IS in 230 patients (mean age 57ys). The occurrence of DF during the following 5years was; NCS-0: 0%, NCS-1: 0%, NCS-2: 1%, NCS-3: 16%, NCS-4: 24%. Occurrence of any of DF, IHD and/or IS was as follows; NCS-0: 0%, NCS-1: 6%, NCS-2: 31%, NCS-3: 54%, NCS-4 59%. There was no death from NSC-0, -1, and -2 groups (n=189), while two from NCS-3 group (n=24) were found dead in a bed or on a driver's seat, and other two from NCS-4 group (n=17) died of sudden cardiac arrest or infection after foot amputation. In summary, the present NCS grading system seems to work satisfactory not only for diagnosis of severity of the current DPN, but also for prognostic prediction of the DPN-related foot and vascular events.

A SENSITIVE MEASURE OF VIBRATION SENSE IN THE CMTNSv2

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For patients with Charcot-Marie-Tooth disease, also known as hereditary motor and sensory neuropathy, the Rasch modified CMTNSv2 is a validated measurement of symptoms and impairment. The score is comprised of nine parameters of a clinical examination, including nerve conduction studies (NCS). Each parameter has an individual score ranging from zero to four, with the composite score having a maximum of 36 prior to Rasch modification. For patients who do not complete a NCS, the CMT Exam Score (CMTESv2) is used, with a maximum score of 28 before Rasch modification. One parameter of the CMTESv2 is the vibration sense. Using a Rydel tuning fork, a care-giver measures vibration sense in a patient's feet, ankles, and knees and a score is determined by the severity of reduced vibration sense. In 80 CMT1A patients, 50% received a score of 3 out of 4, noted by a reduced vibration sense at the knee. In order to capture a more sensitive vibration measurement, we tested ways of taking the total raw score of the Rydel tuning fork at each point of vibration sense, the toe, ankle, and knee bilaterally. Scores range from zero to 48, with 48 reflecting full vibration sense. In this modified measurement, vibration sense scores varied in wider distribution. For CMT1A patients captured in this studied, a modified vibration sense score results in a potentially more sensitive total CMTESv2 score.

ULTRASOUND FINDING IN ACUTE DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

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Diabetic lumbosacral radiculoplexus neuropathies (DLRPN) are usually subacute painful, monophasic, asymmetrical lower limb neuropathies with incomplete recovery due to ischaemic injury and microvasculitis. The diagnosis relies mostly on clinical suspicion and characteristic electromyographic findings. However, in acute phase, neuroimaging has more important diagnostic significance than electrophysiological studies. Here we describe MRI and ultrasound findings in a 59-year-old woman with DLRPN who was diagnosed with diabetes three years ago, but has not received any other treatment. She had a 7-day history of acute-onset severe pain with weakness of muscles innervated by left femoral and obturator nerve and decreased sensation in left L2-L4 dermatome. Nerve conduction studies showed reduced amplitude in left femoral nerve and electromyography showed only increased insertional activity in left iliopsoas muscle and no volitional activity in muscles innervated by left femoral and obturator nerve. Ultrasound revealed increased cross-sectional area (CSA) of left femoral and lateral femoral cutaneous nerve. MRI showed enhancement in left L3, 4 nerve roots and proximal femoral nerve and increased signal intensity in left iliacus and iliopsoas. We diagnosed her with DLRPN and started corticosteroid. Nerve ultrasound has not been previously reported in a patient with DLRPN and this case showed that ultrasound may be the valuable supplement to MRI and electrophysiological studies for the workup of DLRPN.

A COMPARISON OF CLINICAL AND ELECTROPHYSIOLOGICAL PROFILES IN POEMS SYNDROME AND CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome is a rare cause of polyneuropathy. Polyneuropathy is one of the major criteria for the syndrome and usually associated with demyelinating pattern. About 50% of patients with POEMS syndrome revealed only polyneuropathy in the early stages of disease. Therefore, POEMS syndrome is often misdiagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP). The aim of this study is to investigate clinical and electrophysiological findings which could differentiate between POEMS syndrome and CIDP. We reviewed medical records and nerve conduction studies of 58 patients between 2005 and 2016. We enrolled 16 patients with POEMS syndrome and 42 patients with CIDP fulfilling EFNS/PNS criteria for definite CIDP (8 with monoclonal gammopathy of undetermined significance (MGUS), 34 without MGUS). The median age of onset is older in CIDP with MGUS group than in the other groups (CIDP with MGUS 62.0 years, CIDP without MGUS 57.0 years, POEMS 53.0 years; p=0.043). Neuropathic pain is more frequently in POEMS syndrome group (POEMS 50%, CIDP without MGUS 17.6%, CIDP with MGUS 12.5%; p=0.043). POEMS syndrome revealed slower conduction velocity (NCV) (33.3 m/s vs 43.0 m/s; p=0.001), more prolonged F-latency (141.8% vs. 125.0%; p=0.025), and higher terminal latency index (TLI) (0.37 vs. 0.27; p<0.001) in median motor nerve than CIDP without MGUS. Also, POEMS syndrome showed more reduced tibial CMAP amplitude (3.6mV vs. 6.7mV; p=0.014) and more frequently recordable tibial CMAP (59.4% vs. 6.3%; p<0.001) than CIDP without MGUS. On the other hands, CIDP with MGUS group showed much slower NCV (33.5m/s vs. 43.0m/s; p=0.027) than CIDP without MGUS. Compared with POEMS syndrome, CIDP with MGUS group revealed more prolonged terminal latency (4.4ms vs. 7.0ms; p=0.02) and lower TLI (0.37 vs. 0.24; p=0.001). In conclusion, POEMS syndrome demonstrated much slower NCV, less prolonged terminal latency, and higher TLI. Especially, TLI is much higher in POEMS than in CIDP with/without MGUS. Therefore, TLI might be helpful in distinguishing POEMS from CIDP.

PREVALENCE OF PERIPHERAL NEUROPATHY AMONG FREQUENT FLYERS – IS THERE A LINK TO "AEROTOXIC SYNDROME"?

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Cabin air in commercial airliners originates from aircraft engines or auxiliary power units. This bleed air may occasionally be contaminated with hydraulic fluids and engine oil that contains a number of potentially hazardous chemicals including tricresyl phosphate (TCP). Over the last years reports are emerging about aircrew members that experience symptoms such as tingling or burning of extremities in addition to headache, and vertigo. This „aerotoxic syndrome" is controversially discussed in the literature and has been attributed to exposure to organophosphate contaminated cabin air. Since TCP has been associated with peripheral neuropathy we aimed to determine the frequency of peripheral neuropathy among frequent flyers.
84 civilian air crew members and frequent flying passengers (m:f = 35:49, median age 48 years, median exposition time in aircrafts of 12.000 hours) were examined at the University Hospital of Cologne or at the Frankfurt airport (IATA code FRA) by a detailed questionnaire of past medical conditions, a standardized neurological examination and nerve conduction studies of sural, tibial, and ulnar nerves. We identified 5 subjects with clinical and electrophysiological evidence for large fiber peripheral neuropathy. Incidence of peripheral neuropathy was not correlated to exposition time in aircrafts. In addition 11 subjects showed signs of ulnar neuropathy, 13 subjects reported abnormal vibration sensation, 27 subjects suffered from gait imbalance and 50 individuals reported tingling of extremities.
Our study shows a 5.95 % prevalence of large fiber peripheral neuropathy among frequent flyers. Comparison of these data with prevalence rate in an age-matched control group will reveal a possible association of chronic exposure to cabin air and risk for peripheral neuropathy. The high incidence of the symptom tingling in our cohort warrants further studies to determine the risk for small fiber neuropathy in this condition.

IVIg EFFECT IN A WISTAR RAT MODEL OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

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Intravenous Immunoglobulin (IVIg) are human IgG derived from plasma pools of healthy donors. Although there are studies in literature evaluating their effectiveness in different pathological animal models, there are no data about their possible role on Bortezomib (BTZ)-induced peripheral neuropathies. Female Wistar rats were treated following a preventive schedule (BTZ and IVIg co-treatment for 3 and 8 weeks) and a therapeutic schedule (4 weeks of BTZ treatment followed by a 4-week IVIg-BTZ co-treatment). Caudal nerve conduction velocity (NCV), plantar and dynamic tests were performed at different time points. Animals were sacrificed after 3ws (acute phase) or 8ws (chronic phase) and tissue samples (Dorsal Root Ganglias -DRG-, sciatic nerve, caudal nerve, skin) were collected for morphological, morphometrical and immunohistological analysis.In the preventive schedule, IVIg was not able to rescue caudal NCV reduction caused by BTZ neither after 3 nor after 8 weeks of co-treatment. Same results were observed in the therapeutic schedule. On the other hand, the evaluation of mechanical allodynia and cold hyperalgesia showed that IVIg injection protected from BTZ effect in both treatment schedules. Morphometric analysis evidenced that, even if not statistically significant only the preventive schedule has a tendency to protect the caudal nerve from BTZ damage. This result is consistent with the morphological evaluation of the nerve. Also, intra-epidermal nerve fibers density was preserved in the preventive schedule but not in the therapeutic one. Finally, sciatic nerve and DRG macrophage infiltration levels tended to be reduced in the therapeutic schedule and were brought back to ctrl (rats not treated or injected with IVIg alone) levels in the preventive one. In conclusion, we were able to demonstrate for the first time that IVIg treatment especially used as preventive treatment option may reduce BTZ-induced neuropathic painful pointing out the possible role of inflammation in the pathogenesis of this invalidating pathology.

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GENETIC HETEROGENEITY OF MOTOR NEUROPATHIES

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We studied the prevalence, the molecular cause and clinical presentation of hereditary motor neuropathies in a large cohort of patients from the North of England. Detailed neurological and electrophysiological assessments and next generation panel testing or whole exome sequencing were performed in 105 patients with clinical symptoms of distal hereditary motor neuropathy (dHMN, 64 patients), axonal motor neuropathy (motor CMT2, 16 patients) or complex neurological disease predominantly affecting the motor nerves (HMN plus, 25 patients). The prevalence of dHMN is 2.14 affected individuals per 100.000 inhabitants (95% confidence interval: 1.62-2.66) in the North of England. Causative mutations were identified in 26 out of 73 index patients (35.6%). The diagnostic rate in the dHMN subgroup was 32.5%, which is higher than previously reported (20%). We detected a defect of neuromuscular transmission in 7 cases and identified potentially causative mutations in 4 patients with demyelinating multifocal motor neuropathy. Many of the genes were shared between dHMN and motor CMT2, indicating identical disease mechanisms therefore we suggest changing the classification and include dHMN also as a subcategory of CMT. Abnormal neuromuscular transmission in some genetic forms provides a treatable target to develop therapies.

PATIENT ASSISTED INTERVENTION FOR NEUROPATHY: COMPARISON OF TREATMENT IN REAL LIFE SITUATIONS (PAIN-CONTRoLS)

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Cryptogenic sensory polyneuropathy (CSPN) is a common slowly progressive neuropathy that affects adults and presents with significant neuropathic pain for which multiple medications have been tried including antiepileptics, antidepressants, topicals and narcotics. A web based survey among neuromuscular experts suggested pregabalin as being more effective than other medications, however there are presently no comparative studies to assess the most effective medication. The objective of this study was to determine which of the 4 pharmaceutical therapies (pregabalin, duloxetine, nortriptyline or mexiletine) is most effective for neuropathic pain and best tolerated in CSPN. To achieve this objective we performed a prospective randomized open labelled comparative effectiveness adaptive design study of CSPN patients through the patient centered outcomes research institute (PCORI). CSPN patients who fulfilled the inclusion and exclusion criteria were enrolled into this study. Patients underwent a baseline neurological evaluation and randomly assigned to one of the 4 neuropathic medications for 3 months. The primary outcome is the change in likert-like pain scale. The secondary outcomes included NIH pain interference scale, NIH fatigue interference scale, NIH sleep disturbance scale, SF-12 and adverse events. The outcome measures are performed at baseline, month 1, 2 and 3. Statistical analysis using bayesian adaptive design developed by Berry Consultant software will be performed to determine winner and losers (winner = greater than 2 point improvement in pain). Total number of patients to be enrolled is 400. Recruitment has been challenging and a number of recruitment techniques have been used. To date, there have been 292 patients screened, 288 patients randomized from 40 US sites. Anticipated completion of enrollment by June 2017 and end of final patient assessment by September 2017. Interim analysis performed after first 100 patients completed their 3months as part of Bayesian adaptive design analysis and occurs every 13 weeks. The distribution of randomization of patients to the 4 medications at last adaptive design randomization was 29.6% to medication 1, 30% to medication 2 , 20.8% to medication 3 and 19.6% to the 4th medication. This study may give physicians and patients evidence for future management of CSPN patients.

AUTONOMIC SYMPTOMS IN TRANSTHYRETIN AMYLOIDOSIS: AN ANALYSIS OF SYMPTOMATIC SUBJECTS FROM THE THAOS REGISTRY

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Transthyretin amyloidosis (ATTR), which encompasses a group of disorders with significant clinical variability, is caused by transthyretin (TTR) derived amyloid deposition. The clinical aspects of autonomic nervous system involvement in ATTR are only partially known. The ongoing, multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey (THAOS) provides the opportunity to expand our understanding of dysautonomia in ATTR. Data from all symptomatic subjects enrolled in the THAOS registry with a diagnosis of ATTR (cut-off date: January 14, 2016) were assessed for the presence and temporal course of autonomic symptoms, genotype and phenotype associations, and clinical burden according to the frequency and severity of symptoms. Of 2362 symptomatic subjects enrolled in THAOS, 1006 (42.6%) had autonomic symptoms at enrollment including: gastrointestinal

(1399 subjects, 59.2%), urinary (494, 20.9%), erectile dysfunction (329, 13.9%), orthostatic hypotension (223, 9.4%), xerophthalmia (183, 7.7%) and dyshydrosis (93, 3.9%). Subjects with autonomic manifestations, compared with those without, were younger (mean age [standard deviation, SD] of 50.2 [15.1] vs 57.8 [17.7] years), with a longer duration of ATTR symptoms (9.7 [7.1] vs 6.7 [6.5] years). Autonomic dysfunction was less common with wild-type ATTR (27 of 329 subjects, 8.2%) than in mutation groups: Val30Met (824/1471, 56.0%); non-Val30Met/non-cardiac (114/355, 32.1%); and "cardiac mutations" (Val122Ile, Leu111Met, Thr60Ala, or Ile68Leu mutations; 41/207, 19.8%). Similarly, time (mean [SD], years) from first ATTR symptoms to onset of autonomic symptoms, was longest for wild-type ATTR (10.1 [11.4]) followed by "cardiac mutations" (6.3 [7.7]), non-Val30Met/non-cardiac (5.1 [6.7]), and Val30Met (2.8 [4.9]). Autonomic symptoms were present at disease onset in over a third of subjects (355, 35.3%). Autonomic dysfunction was less frequent in subjects with cardiac phenotype (73 of 460 subjects, 15.9%), than with mixed (259/497, 52.1%) or neurologic (765/1171, 65.3%) phenotypes. The burden of autonomic symptoms (mean [SD]) varied by genotype, Val30Met (4.3 [4.0], non-Val30Met/non-cardiac (3.5 [3.1], "cardiac mutations" (2.5 [2.6]), wild-type ATTR (1.6 [1.2]), and by phenotype, mixed (5.5 [5.0]), neurologic (3.9 [3.4]), cardiac (1.7 [1.2]). Dysautonomia is common, and a significant burden, in subjects with hereditary forms of ATTR. Its prevalence is higher in Val30Met than in other genotypes, and in the neurologic or mixed phenotypes.

MOTOR UNIT NUMBER INDEX CORRELATES WITH DISABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A.

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The objective of this study is to assess the usefulness of motor unit number index (MUNIX) technique in Charcot-Marie-Tooth type 1A (CMT1A) disease and to test correlation between MUNIX and clinical impairment. MUNIX technique was performed in abductor pollicis brevis (APB), abductor digiti minimi (ADM) and tibialis anterior (TA) muscles in the non-dominant side. A MUNIX sum score was calculated by adding MUNIX of these 3 muscles. Muscle strength was measured using the MRC (medical research council) scale. Disability was evaluated with several functional scales including CMT neuropathy score version 2 (CMTNSv2) and overall neuropathy limitation scale (ONLS). 33 CMT1A patients with known PMP22 gene duplication were enrolled. The MUNIX of the ADM, APB and TA muscles were correlated with the MRC of the corresponding muscle ($p<0.05$). MUNIX sum score was correlated with clinical scales: CMTNSv2 (r=-0.54, $p<0.01$), ONLS (r=-0.57, $p<0.01$). In conclusion, MUNIX correlates with muscle strength and clinical measurements of disability in CMT1A patients. The MUNIX technique evaluates motor axonal loss and correlates with disability. The MUNIX sum score may be a useful outcome measure of disease progression in CMT1A.

MOTOR UNIT NUMBER INDEX CORRELATES WITH DISABILITY IN CHARCOT-MRI FAT FRACTION OF TIBIALIS ANTERIOR MUSCLE CORRELATES WITH DISABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A.

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The objective of this study was to assess the usefulness of MRI in Charcot-Marie-Tooth type 1A (CMT1A) disease and to test correlation between muscle fat fraction and clinical impairment. MRI was performed in the non-dominant lower limb of CMT1A patients and healthy controls. Fat fraction of tibialis anterior muscle, cross section area and volume of sciatic nerve were determined. Muscle strength of dorsiflexion was measured using a dynamometer. Disability was evaluated with CMT neuropathy score version 2 (CMTNSv2). 15 CMT1A patients with known PMP22 gene duplication were enrolled. Fat fraction of tibialis anterior muscle was significantly increased in patients compared to healthy controls. It was correlated with muscle strength (r=-0.62, $p<0.05$) and CMTNSv2 score (r=-0.65, $p<0.05$). Cross section area and volume of sciatic nerve were significantly increased in patients compared to healthy controls. In conclusion MRI fat fraction correlates with muscle strength and clinical measurement of disability in CMT1A patients. It may thus be a useful outcome measure of disease progression in CMT1A.

OVERALL DISEASE IMPACT OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

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There is a complete lack of data about epidemiological and clinical features of chronic inflammatory demyelinating polyneuropathy (CIDP) in Serbia and surrounding countries. Furthermore, there is a striking scarcity of information about quality of life (QoL) in CIDP patients and all QoL studies have been conducted in countries with high standards of health care. In August 2016 we have designed the INeSS (Inflammatory Neuropathy Study of Serbia) in order to comprise as many patients with CIDP from Serbia, Republic of Srpska (Bosnia and Herzegovina) and Montenegro covering population of more than nine million people. Our first aim is to analyze overall impact of CIDP on physical, mental and social areas of life measured with generic, symptom specific and disease specific questionnaires – SF-36, INQoL and CAP-PRI, respectively. Furthermore, we aim to analyze influence of the disease on patients' working status and presence of depressive mood measured by Beck's inventory. Following features of patients are included: sociodemographic data, clinical aspects of the disease, level of disability, severity of sensory symptoms, presence of comorbidities, electrophysiological characteristics, as well as fatigue, autonomic symptoms and neuropathic pain. We intend to define the most significant predictors of decreased QoL in order to focus on patients with the highest risk and to improve care of CIDP. We also want to see if CIDP patients in complete remission as per clinical findings still have reduced quality of life. We have recruited 58 patient so far and we expect to include around 80 subjects overall. We will present the first data of the study at the PNS meeting 2017.

NEUROPHYSIOLOGICAL FINDINGS IN ASYMPTOMATIC STAGE OF FAMILIAL AMYLOID NEUROPATHY: A CASE CONTROL STUDY

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Familial amyloid neuropathy (FAP) is a life-threatening disease of autosomal dominant inheritance due to transthyretin (TTR) gene mutation, a liver-produced protein. Current treatments slow down its natural course and are indicated from the very first objective symptoms. We aimed to evaluate two neurophysiological markers: sympathetic skin response (SSR) and heart rate variability (HRV) in the early detection of sympathetic damages due to FAP. SSR and HRV were assessed in 21 TTR gene mutated patients with neither clinic nor electroneuromyographic abnormalities and 21 controls matched on gender and age. Cases were recruited consecutively from current care in the French Reference Center for Rare Diseases of Bicetre University Hospital. SSR was recorded on the two palms and on the sole of the left foot with 3 to 7 stimulations between 15 and 20 mA. HRV was registered during three conditions of 60 seconds each: normal breathing, deep breathing (6 cycles of 5 seconds of inspiration and 5 seconds of expiration) and Valsalva manoeuver during 15 seconds. Valsalva ratio, defined by the ratio between the longest and shortest RR intervals, was significantly higher in the control groups after Bonferroni correction (means of 1.556 and 1.929, respectively, $p< 0.0001$). There was no significant difference between the two groups for any SSR parameter, although means of amplitudes were systematically higher in controls than among cases. Our results confirm that autonomic nervous fibers are damaged early in both clinical and electroneuromyographic asymptomatic patients mutated on the TTR gene. Valsalva ratio seemed to be the most discriminative marker. Long-term follow-up with test repetition and confrontation with cardiologic assessment will help to precise how these tests could be used in current care. They might help to identify high risk patients to propose them an appropriate early treatment and could be used to follow treatment efficacy.

RECURRENT PERIPHERAL AND CENTRAL DEMYELINATION IN A SERONEGATIVE PATIENT

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The content and antigenic properties of central and peripheral myelin are different therefore; simultaneous autoimmune central and peripheral demyelination is an extremely rare condition. Here we present a unique patient diagnosed with recurrent acute immune mediated central and peripheral demyelination. Eighteen year-old man admitted due to generalized weakness with respiratory insufficiency. The electrophysiological evaluation was compatible with acute inflammatory demyelinating polyneuropathy (AIDP) and treated with intravenous immunoglobulin (IVIg). In the second week of the treatment he started to suffer from vision loss in left eye. The cranial magnetic resonance imaging (MRI) showed multiple subcortical lesions with contrast enhancement compatible with acute demyelinating encephalomyelitis (ADEM). His complaint benefited from 5 days 1000 mg methylprednisolone. Twelve years later, he referred because of generalized weakness with respiratory insufficiency. Bilateral shoulder abduction was 2, elbow flexion and extension were 3, hip flexion was 3 and foot dorsiflexion was 4 according to Medical Research Council scale. He was diagnosed with AIDP. His cranial MRI depicted right cerebellar, temporal bilateral frontoparietal subcortical contrast enhanced active lesions. IgG index was high as 1 and oligoclonal band was positive and cerebrospinal fluid (CSF) protein was 305 mg/dL. Serum and CSF anti-MOG and anti-neurofascin antibodies were both

negative. The patient was successfully treated with plasma exchange. His follow-up MRI after 3 months was normal. Previously five patients with both multiple sclerosis and chronic inflammatory demyelinating polyradiculoneuropathy were followed in our institute, all were negative for anti-neurofascin. However, there are very few reports of patients with simultaneous Guillain-Barré Syndrome and ADEM. Our report defers from these patients due to recurrent course.

WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS (ATTR-WT) AND PERIPHERAL NEUROPATHY

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Familial amyloidotic polyneuropathy (FAP) was originally characterized by Andrade as an axonal neuropathy which subsequently was found to be associated with a number of mutations in the plasma protein transthyretin (previously named prealbumin). It is now recognized that cardiomyopathy may be a significant factor in a majority of patients with the hereditary form of transthyretin amyloidosis (FAP) and many of the transthyretin (TTR) mutations are associated with cardiomyopathy with no or minimal signs of peripheral neuropathy. ATTR-WT also called senile cardiac amyloidosis and senile systemic amyloidosis is recognized as late-onset, usually in the 8^{th} or 9^{th} decade of life, and the fact that the majority of patients are males. Transthyretin neuropathy proven by nerve biopsy has been rarely reported in this population. Here we report our experience with patients having ATTR-WT characterized by cardiomyopathy but also with varying degrees of peripheral neuropathy. Clinically, the neuropathy appears as typical axonal or mixed axonal/demyelinating neuropathy as is seen in FAP. Pathologically, two types of TTR deposition have been found, (1) intraneural TTR amyloid deposits as seen in FAP are present in some patients and (2) other patients have extensive vascular deposition of amyloid in both perineural arteries and veins without deposits within nerve trunks. In conclusion, peripheral neuropathy may definitely be a part of the ATTR-WT clinical presentation and with the increase in numbers of ATTR-WT cardiomyopathy patients being identified, it is important to ascertain whether any evidence of peripheral neuropathy is due to the amyloidosis and not to compounding syndromes such as diabetes mellitus type II.

PERIPHERAL NEUROTOXICITY IN OXALIPLATIN RETREATMENT IN COLORECTAL CANCER PATIENTS

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Oxaliplatin (OXA) is the first-line chemotherapy agent in the treatment of colorectal cancer (CRC). OXA-induced peripheral neuropathy is the most frequent long-term side-effect. Retreatment with OXA is frequently considered in patients as salvage treatment. Patients receiving OXA-based chemotherapy regimen at least twice at our institution between 2000 and 2016 were reviewed. The aim of this study was to investigate whether retreatment with OXA increases the risk of developing or worsening previous OXA-induced peripheral neuropathy. The severity of neuropathy was measured by National Cancer Institute-Common Toxicity Criteria (NCI), Total Neuropathy Score (TNS)© and nerve conduction studies. One hundred twenty-five CRC patients were included. Median age was 64 [25-84] years. After first-line OXA-based chemotherapy, 67.2% of patients developed neuropathy according NCI, after a median of 11 [1-17] cycles. Severity of neuropathy was grade 1 (26.7%), grade 2 (31%), and grade 3 (9.5%). Median time to retreatment with OXA was 30 [11-90] months. Frequencies of neuropathy before retreatment were as follows: 60.2% grade 0, 32.4% grade 1, and 7.4% grade 2. After retreatment, severities of neuropathy were 34.4 % grade 1 and 38.4% grade 2. No patient developed grade 3. 22.4% of patients did not develop neuropathy. Peripheral neuropathy was the reason for stopping prematurely treatment after first-line and retreatment in 20.5% and 16.4% of patients, respectively. Worsening of previous NCI score was observed in 30.8% of patients. The great majority of patients (69.2%) remained within the same NCI score than before retreatment after median 8 [1-14] cycles. Among those patients that did not develop neuropathy after first treatment (n=39), only 11 and 5 patients developed grade 1 and 2, respectively, after a median of 7 [1-12] cycles. Among those patients who initially developed grade 2 and 3 neuropathy, no differences in TNSc© scores just before and after finishing retreatment with OXA were identified (6 [3-11] vs 6 [4-12], p=0.214). Retreatment with OXA in CRC patients is a feasible option even in patients who developed moderate or severe neuropathy previously. Lack of worsening of previous neuropathy is observed in the great majority of patients. Neurological monitoring of patients candidates to retreatment with OXA should be considered.

SENSORY SMALL FIBERS IMPLICATION ON INFLAMMATION REGULATION DURING SKIN PRESSURE ULCER DEVELOPMENT IN MICE

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Prolonged pressure and the resulting local ischemia are widely accepted as the primary etiology of skin pressure ulcers (PUs) but precise mechanisms of their formation remain unclear. In this study, we wanted to study the potential role of sensory small nerve fibers in regulation of inflammation during PUs formation. To achieve this goal, we developed a mouse model of a purely sensory neuropathy and this was induced by resiniferatoxin (RTX). In this model, seven days after a single injection of RTX (50µg/kg; IP), mice present a thermal and mechanical hypoalgesia associated with large Substance P (SP) and Calcitonin Gene-Related Peptide (CGRP) depletion without neurodegeneration. This model mimic quite well what is observed in early stages of sensory nerve fiber defect. Studies have shown that SP and CGRP are involved in cutaneous inflammation regulation. In fact, these neuropeptides are released by sensory fibers and are pro-inflammatory mainly through recruitment of immune cells and vasodilation. Thus, we studied gene expression of pro and anti-inflammatory cytokines by a RNA Array approach during PUs formation in control and RTX mice. Seven days after a single injection of RTX, epidermis, dermis and subcutaneous tissue layer were pinched with magnetic plates during 12 hours. Pressure induced a stage 3 PUs. Gene expression was evaluated in each compressed area 24h after pressure. Results showed mainly a down-regulation of gene expression in PUs of RTX mice compared to control mice. A decrease of CGRP/SP in skin sensory small fiber increased PUs formation associated with an increase of interleukins (IL)-1, IL-4, IL-11 and IL-20 expression and a decrease of IL-16 expression in RTX mice. Supplementary experiments with RT-qPCR for each cytokine will be necessary to confirm these preliminary results.
These observations suggest a CGRP/SP role in regulation of cytokines expression during PUs formation. The new inflammatory profile exhibited in this study might help in the design of new treatments improving the quality of life of neuropathic patients prone to developing bedsores.

REVERSAL OF PAINFUL DIABETIC NEUROPATHY BY CONTROL OF NOCICEPTOR EXCITABILITY.

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Painful diabetic neuropathy (PDN) is one of the most common and intractable symptoms of diabetes, affecting 25% of diabetic patients. The hallmarks of PDN are neuropathic pain and small fiber degeneration, manifested by the loss of dorsal root ganglion (DRG) nociceptor axons. Neuropathic pain is associated with nociceptor hyper-excitability in the absence of physiologically appropriate stimuli. In states of neuropathic pain, DRG nociceptors become increasingly responsive to a variety of excitatory influences, including inflammatory cytokines. In particular, we have shown that stromal cell derived factor-1 (SDF-1) and its receptor CXCR4 are necessary for the generation of neuropathic pain in mouse models of PDN. However, the molecular mechanisms leading to the hyper-excitability of DRG nociceptors in PDN are unknown, as are the mechanisms leading to small fiber degeneration. This fundamental gap in our knowledge represents a critical barrier to progress in developing novel therapeutic approaches for PDN. The objective of this study is to identify the molecular cascade linking CXCR4/SDF-1 chemokine signaling to DRG nociceptor hyper-excitability, neuropathic pain, and small fiber degeneration in PDN. DRG nociceptors can be identified by a series of molecular markers, including expression of the sodium channel $Na_v1.8$. Indeed, >90% of $Na_v1.8$-expressing DRG neurons are nociceptors. Feeding mice a high fat diet (HFD) for several weeks induces glucose intolerance, obesity, and mechanical allodynia, a particular pain hypersensitivity associated with PDN. Using the HFD model combined with DREADD receptor technology, we have shown that reducing excitability of $Na_v1.8$-expressing neurons prevents and reverse neuropathic pain, neuronal calcium overload, mitochondrial dysfunction, and small fiber degeneration. Furthermore, we have shown that CXCR4 receptors are necessary for neuropathic pain and small fiber degeneration in PDN. Taken together these data demonstrate that $Na_v1.8$ nociceptor hyperexcitability in PDN is driven through the activation of CXCR4 receptors. Inhibition of hyperexcitability can prevent and reverse the development of PDN. Furthermore, these observations will advance our understanding as to how changes in excitability, calcium influx, and mitochondrial dysfunction in nociceptors contribute to neuropathic pain and small fiber degeneration in PDN, which is a critical barrier to progression for effective and disease modifying treatment for PDN.

COMPARISON OF TWO-YEAR RESPONSE TO LENALIDOMIDE OR PERIPHERAL BLOOD STEM-CELL TRANSPLANTATION IN PATIENTS WITH POEMS

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POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes) syndrome is an unusual multisystem disease with neurological disability due to a severe disabling polyneuropathy, with high mortality by multiorgan failure. Peripheral blood stem cell transplantation (PBSCT) is considered the treatment of choice for POEMS while lenalidomide is the most promising therapy for patients not eligible for PBSCT. The aim of the present study was to compare the long-term effects on clinical, biological and neurophysiologic parameters in patients with POEMS treated with Lenalidomide or PBSCT. The clinical, biological and neurophysiologic data were reviewed in 15 POEMS patients treated with PBSCT (n: 6) or lenalidomide (n: 9). The MRC sumscore on 16 muscles, ONLS scale, VEGF serum levels and nerve conduction studies were assessed before (T0) and after 1 (T1) and 2 years (T2) of treatment and the differences were compared using ANOVA. Combining the two groups of patients, there was a significant improvement after treatment in the mean MRC sumscore (T0 = 65±15; T1 = 69±11; T2 = 71±8; p = 0.000), in the mean ONLS score (T0 = 5.6+2.6; T1 = 3.6+1.9; T2 = 3.5+2; p = 0.000), in the ulnar mean distal motor latency (T0 = 3.8±1.2 msec; T1 = 3.3±0.4 msec; T2 = 3.0±0.4 msec; p = 0.02), distal compound muscle action potentials amplitude (T0 = 6.8±2.8 mV; T1 = 7.2±3.2mV; T2 = 7.4±2.9mV; p = 0.0000), motor conduction velocity (T0 = 37.4± 10.7 m/sec; T1 = 43±9 m/sec; T2 = 47.9±9.3 m/sec; p=0.0003) and serum VEGF levels (T0 vs T1: p = 0.011; T0 vs T2: p = 0.010). The difference was also significant when we separately analyzed patients treated with lenalidomide and PBSCT and there was no difference between the two groups in any of the analyzed parameters. Treatment with PBSCT and lenalidomide significantly and similarly improved clinical, biological and neurophysiologic parameters in patients with POEMS syndrome up to two years. Since PBSCT may not be suitable for all patients, Lenalidomide may represent an effective and a valuable alternative in these patients or in those relapsing after PBSCT inducing a prolonged clinical, biological and neurophysiologic improvement.

MUTATIONAL BURDEN ANALYSIS IN INHERITED PERIPHERAL NEUROPATHIES

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Inherited peripheral neuropathies are clinically and genetically heterogeneous diseases that can cause distal muscular atrophy and sensory loss. Alleles in over one hundred different genes have been shown to cause peripheral neuropathies; yet, greater than 50% of axonal neuropathy patients do not receive a genetic diagnosis. Large scale exome studies are now beginning to be sufficiently powered to perform mutational burden analysis. This approach compares damaging allele frequencies of CMT cases with a control group to identify additional causes for neuropathies. This approach will also identify genes that require an oligogenic inheritance to cause a phenotype. In a deviation from the classic linkage-based and heuristic variant filtering approaches to gene identification, we are performing burden analyses in a large cohort of 382 CMT families. In 113 known neuropathy genes, we saw that neuropathy cases carried on average 7.04 rare, non-synonymous variants, while 927 unrelated non-neuropathy controls harbored 5.76 variants (p=4.23E-06, Mann-Whiney U-test). Enrichment of rare, non-synonymous variants in CMT disease genes within inherited peripheral neuropathy cases suggests the presence of multiple weaker alleles in individual patients. We also performed an unbiased exome-wide gene-based burden analysis and ranked genes after multiple testing correction. Several new candidate genes were identified that need further follow up conformational studies. A number of known CMT and related genes were observed in the list of top candidates. We are currently analyzing additional aspects of this sample and are actively seeking more CMT exomes to enlarge our study. In summary, statistical methods traditionally reserved for more 'common' phenotypes' increasingly are becoming available for rare disease genetics.

EFFECTS OF MONASTROL IN BORTEZOMIB INDUCED PERIPHERAL NEUROPATHY

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Peripheral neuropathy is a common side effect of bortezomib. There is experimental evidence that bortezomib induces axonal degeneration by altering microtubule stabilization and axonal transport. Based on results from previous studies that the kinesin-5 inhibitor monastrol enhances axonal transport and improves neuronal regeneration, we assessed the utility of monastrol to protect against bortezomib induced neuropathy.
C57BL/6 mice were treated with bortezomib alone or in combination with monastrol. Neuropathic changes were assessed by nerve conduction studies and histological analysis. Analysis of axonal morphology was performed with light and electron microscopy. Anti-neoplastic properties of monastrol alone and in combination with bortezomib were assessed in different blood cancer cell lines.
Prolonged treatment with bortezomib induced a sensory neuropathy in mice. Significant changes in axonal morphology correlated with reduced function of peripheral nerves. The administration of monastrol substantially ameliorated morphological features of axonal alterations and sensory neuropathy.

Cytotoxicity studies in blood cancer cell lines showed no interference of monastrol with the cytostatic effects of bortezomib.
Our data indicate that monastrol may alleviate bortezomib induced neuropathy. The favorable cytotoxic profile of monastrol makes it an interesting candidate as neuroprotective agent to prevent bortezomib-induced neuropathy.

MUTATION IN GLYCYL-tRNA SYNTHETASE IMPAIR MITOCHONDRIAL METABOLISM IN NEURONS

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While autosomal dominant mutations in *GARS*, encoding the glycyl-tRNA synthetase, have been identified in patients with Charcot–Marie–Tooth peripheral neuropathy (CMT2D) and distal spinal muscular atrophy type V (dSMA-V), autosomal recessive mutations cause mitochondrial disease affecting skeletal muscle and heart. GARS is a bi-functional enzyme and it is responsible for normal protein translation both in mitochondria and the cytoplasm. In this study we have focused on the mitochondrial function of the GARS by investigating a mouse model ($Gars^{C210R)}$, human fibroblasts and induced neuronal progenitor cell lines (iNPCs). Mild mitochondrial abnormalities were detected in skeletal muscle of the $Gars^{C210R}$ mice while no other tissues were affected. Control and patient fibroblasts harboring *GARS* mutation were directly converted into iNPCs. We identified tissue specific impairment of mitochondrial function in neuronal cells carrying not only recessive but also dominant *GARS* mutations, suggesting neuron-specific effects of mitochondrial alterations.Comparative proteomic analysis of iNPCs showed significant changes in 41 mitochondrial proteins. Furthermore, the reduction of the vesicle-associated membrane protein-associated protein B (VAPB) and its downstream pathways in GARS-deficient iNPCs suggests that altered mitochondria-associated endoplasmic reticulum (ER) membranes (MAM) may also contribute to the motor neuropathy.

MITOCHONDRIAL OXODICARBOXYLATE CARRIER DEFICIENCY: METABOLIC MODELLING IDENTIFIES DISEASE MECHANISM

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Members of the mitochondrial carrier family (SLC25) transport nucleotides, keto acids, amino acids, fatty acids, co-factors and inorganic ions across the mitochondrial inner membrane. Several inherited diseases with very variable clinical presentations are associated with dysfunctional mitochondrial carriers. We report a patient with childhood-onset spinal muscular atrophy and mitochondrial myopathy caused by a homozygous mutation in *SLC25A21*, encoding the mitochondrial oxodicarboxylate carrier (ODC). The mutation renders the carrier dysfunctional and, consequently, 2-oxoadipate cannot be imported into the mitochondrial matrix. Computer modelling of the metabolic defect caused by the mutation predicted that the impaired transport leads to accumulation of 2-oxoadipate, pipecolic acid and the known neurotoxin quinolinic acid, which were precisely confirmed by targeted metabolomics in serum and urine. Exposure of 2-oxoadipate and quinolinic acid reduced the level of mitochondrial complexes in SH-SY5Y cells *in-vitro* suggesting a possible pathomechanism. Here we demonstrate that 2-oxoadipate and quinolinic acid are toxic for spinal motor neurons and their increased levels may contribute to neuropathy.

A KNOCK-IN / KNOCK-OUT MOUSE MODEL FOR SMALL HEAT SHOCK PROTEIN HSPB8 MIMICKING DISTAL HEREDITARY MOTOR NEUROPATHY AND MYOFIBRILLAR MYOPATHY

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Patients with distal hereditary motor neuropathy (dHMN) develop progressive motor impairments, weakness and atrophy of distal limb muscles. Since our first description of the K141N missense mutation in the small heat shock protein HSPB8, a number of additional dHMN patients and families have been reported. Interestingly, most mutations target the same amino acid residue (K141E, K141M, K141N, K141T) in the highly conserved α-crystallin domain of the HSPB8 protein. The spectrum of diseases caused by mutations in the *HSPB8* gene was

recently expanded to distal myopathy. HSPB8 is ubiquitously expressed, but is highly expressed in motor neurons and muscles. The HSPB8 is a chaperone that participates in clearing misfolded poly-Q containing proteins such as mutant *huntingtin* and *ataxin-3* involved in respectively Huntington's disease and spino-cerebellar ataxia. HSPB8 directly interacts with the co-chaperone BAG3 and their role in chaperone-assisted selective autophagy is well described. To delineate the molecular deficits and functional consequences of HSPB8 mutations we generated a knock-in (KI) mouse model for the K141N missense mutation mimicking the neuropathy phenotype. We observed that homozygous mutant mice ($HspB8^{K141N/K141N}$) develop a progressive axonopathy, with decreased compound motor action potential amplitudes, and loss of large and medium myelinated axons. This results in locomotor deficits with an impaired performance at the rotarod and grip strength tests. At the ultrastructural level, the *HspB8*-KI model displays severe signs of axon degeneration and a clear myofibrillar myopathy, as observed in some patients with HSPB8 mutations. Interestingly, HspB8 positive aggregates were found in the sciatic nerve and gastrocnemius muscle of our mutant mice. Additionally, our model allowed us to generate HSPB8 knock-out (KO) mice using the same targeting vector. Strikingly, the homozygous *HspB8*-KO animals do not show any sign of axonopathy and display a much milder myopathy than the *HspB8*-KI animals. These data suggest that part of the pathomechanisms is due to toxic gain-of-function of the mutant protein.

RABBIT ANTI-FGFR3 ANTIBODIES INDUCE NEURON CELL DEATH AND MODULATE FGFR3 AND NMDA AND AMPA RECEPTORS THROUGH THE P38-MAP KINASE PATHWAY.

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Dysimmune sensory neuronopathies (SNN) depend on neuron cell death induced by an inflammatory reaction in dorsal root ganglia. We have recently identified the intracellular tyrosine kinase (TRK) domain of the Fibroblast Growth Factor Receptor-3 (FGFR3) as the target of antibodies in a subset of patients with non paraneoplastic SNN. FGFR3 is one of the four FGFRs and has been involved in sensory neurons maintenance during development and cell death induction after axotomy. FGFRs ligand fixation results in the activation of several intracellular pathways through adaptator protein interactions with the TRK domain. In particular Ras activation may lead to cell proliferation or apoptosis through Erk1/2 or p38 MAP kinase signaling. The p38 MAPK pathway is also involved in neuronal cell death induced by NMDA and AMPA receptor activation. As FGFR3 is a cell surface protein, human antibodies may interfere with the receptor functioning as a growing number of evidence has showed with other cell surface antibodies in neurological diseases. To test this hypothesis we developed an in vitro model using FVBN mice cortical neurons culture exposed to a rabbit polyclonal antibody reacting with the TRK domain of FGFR3. Comparatively to normal rabbit IgGs, the FGFR3 antibody induced neuron cell death in a dose dependent manner. Neuron cells were exposed to FGFR3 antibody concentration leading to 10-20 % cell death in absence or presence of the p38 MAPK inhibitor SB203580 and the expression of FGFR3, GLUR1 subunit of AMPA receptors and NR1 subunit of NMDA receptor was measured by quantitative RT-qPCR. The FGFR3 antibody induced an upregulation of FGFR3 while the GLUR1 and NR1 subunits were modulated. These changes were prevented in presence of SB203580. These preliminary results indicate that anti-FGFR3 IgGs may interfere with the functioning of the intracellular domain of the protein and the expression of NMDA and AMPA receptors through the p39 MAP kinase pathway. This model may be used to test the effect of human anti-FGFR3 IgGs in vitro.

NOVEL, LIKELY PATHOGENIC, SEQUENCE VARIANTS IN HEREDITARY NEUROPATHY GENES

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Next-generation sequencing (NGS) has during the last years entered the clinical diagnostics. NGS has proven to be very efficient in the diagnostics of disorders where multiple genes can be involved. Our NGS-based targeted gene panel consists of 99 hereditary neuropathy genes, i.e. mostly Charcot-Marie-Tooth genes. This study is a retrospective study of clinic samples received between May 1 2014 and February 1 2017. We describe the identified novel likely pathogenic sequence variants, according to International Guidelines. In this period we identified novel, not previously described, likely pathogenic sequence variants in the following genes: *AARS, FGD4, GAN, HINT1, LITAF, LRSAM1, MME, MPZ, NEFL, PMP22, SBF1, SH3TC2* and *YARS.* There is now a large range of genes causing hereditary peripheral neuropathies and many likely pathogenic sequence variants. Likely pathogenic sequence variants are not only identified in old well established neuropathy genes but also in the newer genes like *MME*.

MODELLING BROWN-VIALETTO-VAN LAERE SYNDROME IN *C. ELEGANS*

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Brown-Vialetto-Van Laere syndrome (BVVL) is an autosomal recessive neurodegenerative disease caused by mutations in *SLC52A2* and *SLC52A3*, which encode the riboflavin transporters RFVT2 and RFVT3. Patients with RFVT2 deficiency exhibit proximal and distal limb weakness, sensory ataxia, diaphragmatic paralysis, optic atrophy, sensorineural deafness and bulbar palsy. Riboflavin is critical for the biosynthesis of flavin mononucleotide and flavin adenine dinucleotide, essential cofactors for carbohydrate, amino-acid and lipid metabolism. Mutations in *SLC52A2* reduce or abolish RFVT2 expression resulting in impaired riboflavin uptake into sensory and motor neurons. High-dose riboflavin treatment can improve or stabilise a patient's condition, however the optimum dose and long term effects of riboflavin treatment, and disease pathomechanisms remains poorly understood. To further understand the pathophysiological consequences of *SLC52A2* mutations, we propose developing an animal model for BVVL. *Caenorhabditis elegans* (*C. elegans*) are small round transparent nematodes extensively used for studying the genetics and molecular biology of neurodegenerative diseases. There are two *C. elegans* riboflavin transporter genes, *rft-1* and *rft-2*. Based on protein sequence homologies and expression profiles for both genes, RFT-1 is the ortholog of RFVT2. The expression of RFT-1 is regulated by riboflavin availability and knock-down of the *rft-1* gene by siRNA perturbs *C. elegans* development. Our aim is to develop a knock-in *C. elegans* model of BVVL. Human RFVT2 and *C. elegans* RFT-1 protein sequences were aligned with Clustal Omega to identify conserved amino acid residues associated with BVVL mutations. The amino acid involving the L339P RFVT2 mutation is conserved in RFT-1 (residue L324). To create our model, we will introduce the L324P RFT-1 mutation into the *rft-1* locus in *C. elegans* genomic DNA using CRISPR/Cas-9 technology. This BVVL *C. elegans* model will allow us to explore the pathogenic consequences of RFVT2 deficiency underlying motor nerve degeneration and to evaluate drug therapy regimes by determining the optimal riboflavin dose and treatment initiation, and trialing other compounds that may improve benefits seen with riboflavin supplementation.

EFFECTIVE THERAPEUTIC EFFECT OF HUMAN IMMUNOGLOBUMIN AND A RECOMBINANT Fc PORTION ON A RAT MODEL FOR CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune-mediated inflammatory disease of the peripheral nervous system. CIDP can present chronic progressive or relapsing-remitting courses and can predominantly affect motor but also sensory nerve fibers causing weakness of proximal and distal muscles. It represents the most common chronic autoimmune neuropathy and is pathologically characterized by focal inflammatory-mediated demyelination followed by axonal degeneration. Recently, we have developed a new animal model for CIDP, the chronic-EAN, induced in Lewis rats by active immunization with S-palmitoylated P0(180-199) peptide. This model fulfills electrophysiological criteria of demyelination with axonal degeneration, a result confirmed by immunohistopathology. The late phase of the chronic disease is characterized by an accumulation of IL-17$^+$ cells and macrophages in sciatic nerves and as well as high serum IL-17 levels. It is a reliable and reproducible animal model for CIDP that can now be used for translational drug studies for chronic human autoimmune-mediated inflammatory diseases of the peripheral nervous system, particularly CIDP, for which, there is a real need for new immunotherapies. The aim of this study was to test the therapeutic efficacy of IVIg and a recombinant Fc fragment (FcRec) in this new CIDP animal model. Treatments with IVIg and FcRec proved effective in preventing further progression of CIDP in rats. The therapeutic treatments not only decreased the maximal clinical scores of the CIDP rats compared to albumin treatment but also abolished the disease chronicity. Interestingly, a better efficacy of FcRec treatment compared to IVIg was demonstrated at histological level, with the myelinated fibers well preserved and the greatly reduced accumulation of macrophages and IL-17$^+$ cells in sciatic nerves. IVIg and FcRec therapeutic activities in this model can also be followed by measurement of IL-17 and anti-P0(180-199) antibodies in the serum and could therefore be used as biological markers. The current study provides for the first time direct evidence that IVIg is effective in the treatment of CIDP rats and suggests that a novel FcRec compound is more effective than IVIg. It will contribute to the development of more effective and safer drugs for the treatment of autoimmune peripheral neuropathies like CIDP.

INVESTIGATION OF THE VARIATION OF MOTOR CONDUCTION VELOCITY BY USING HOPF`S COLLISION TECHNIQUE IN CIDP PATIENTS

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A prompt and correct diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is very important to initiate an appropriate therapy in CIDP patients. Normally, conventional nerve conductions studies (NCS) are used to detect demyelination. But especially in cases of “probable” or “possible” CIDP according to the EFNS criteria, additional electrodiagnostic parameters indicating demyelination more precisely are desirable. In our study, we examined the variation of motor nerve conduction velocity by applying Hopf`s collision technique in CIDP patients. The collision technique was performed at the ulnar nerve of 24 CIDP patients and at a control group of 37 healthy individuals. Each time, one measurement with supramaximal stimulation according to the conventional NCS and another measurement with 50% enhanced stimulation intensity were conducted. We analyzed the results with special consideration of minimal and maximal fiber velocities and of the velocity with maximal fiber proportion. As a result, we detected statistically significant differences between CIDP patients and controls in all these parameters. Compared with controls, CIDP patients had slower minimal and maximal fiber velocities and also the spectrum of motor conduction velocities was definitively shifted to slower velocities. Slower minimal conduction velocities could be detected in some CIDP patients by using the enhanced stimulation intensity. Interestingly, in some CIDP patients the conventional ulnar NCS were normal, but the collision technique showed fibers with a conduction velocity of less than 35 m/s, indicating demyelination. To our knowledge, this is the first study using Hopf`s collision technique systematically in CIDP patients. Significant differences between the variation of ulnar motor nerve conduction velocity of CIDP patients and controls could be detected. This method also showed signs of demyelination in some CIDP patients with normal ulnar NCV. By enhancing stimulation intensity above the threshold of supramaximal stimulation in conventional NCS, the collision technique may be even more valuable.

TREATMENT RELATED FLUCTUATIONS AND ACUTE-ONSET CIDP IN THE IGOS COHORT.

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The clinical course of Guillain-Barré syndrome (GBS) is highly variable and some patients may develop treatment-related fluctuations (TRFs) as an indication of ongoing disease activity and temporary treatment effect. Other patients present as GBS, but subsequently develop repetitive relapses as an indication of acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP). This distinction is important because treatment may differ. We determined the frequency and clinical presentation of patients with GBS-TRF and A-CIDP in the first 1000 patients included in the International GBS Outcome Study (IGOS) with a follow-up of at least 12 months. Thirty-eight patients (4%) were excluded because of alternative diagnoses. Of the remaining 962 patients, 40 (5%) had at least one TRF, 35 (4%) had A-CIDP. Preliminary analysis showed no significant differences between the 3 groups (total-GBS, GBS-TRF and A-CIDP) for sex, age, sensory symptoms, cerebrospinal fluid results and mechanical ventilation. A-CIDP patients had a median age of 54 years (IQR 40-70), 66% was male, and all patients were treated in the acute phase of the disease (intravenous immunoglobulins (IVIg) (31), plasma-exchange (PE) (3) or methylprednisolone (MP) (1)). GBS-TRF patients has a median age of 57 years (IQR 40-67), 48% was male and all patients received treatment (IVIg (35) and PE (5). GBS-TRF patients showed more antecedent events (78% versus 49%, p=0.011), a higher GBS disability score (≥3) at nadir (100% versus 86%, p=0.018) and less frequently developed ataxia (32% versus 71%, p=0.001) than patients with A-CIDP. Onset to nadir was longer in A-CIDP than in GBS-TRF (33 days (IQR 12-60) versus 17 days (IQR 8-33), p=0.023) and the total GBS group (9 days (IQR 5-13), p=0.000). The time until the first clinical deterioration tends to be longer in the A-CIDP patients (median 41 days (IQR 26-56) versus median 31 days (IQR 20-33) in the GBS-TRF group, not significant). The diagnosis A-CIDP was made after a median of 69 days (IQR 53-111). In conclusion, this first analysis identified distinctive characteristics of GBS-TRF and A-CIDP in support of a different pathogenesis that may help with early identification of these disorders in clinical practice. Additional results will be presented at the conference.

INTERNATIONAL CIDP OUTCOME STUDY (ICOS): A PROSPECTIVE STUDY ON CLINICAL AND BIOLOGICAL PREDICTORS OF DISEASE COURSE AND OUTCOME

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a disorder with a highly diverse clinical presentation, electrophysiological phenotype, response to treatment and outcome. This heterogeneity may indicate the presence of distinct subtypes of CIDP, which may have a different pathogenesis and require more personalized treatment. The International CIDP Outcome Study (ICOS) is a prospective, observational, international multi-center study that aims to describe this variation in clinical and electrophysiological subtypes and to

define the clinical and biological determinants of these subtypes, disease activity, treatment response and outcome. In addition ICOS aims to provide an infrastructure for conducting new (therapeutic) studies in CIDP, similar to the International GBS Outcome Study (IGOS). All patients fulfilling the EFNS/PNS (2010) diagnostic criteria for CIDP can be included in ICOS, independent of age, duration and severity of disease or treatment. We collect information on neurological deficits, diagnostic characteristics, various validated clinical outcome measures, previous and current treatment and we collect biomaterials (DNA, cerebrospinal fluid, nerve biopsies and repeated serum samples). ICOS was started as a pilot study in 3 Dutch University Centers. By February 2017, 78 patients were included in ICOS, 35 patients recently diagnosed with CIDP and 43 previously diagnosed patients. Included were 49 (63%) males and 29 (37%) females with a median age of 63 years (IQR 52 - 71). The current cohort consists of 52 classic (sensory-motor) CIDP, 16 MADSAM and 5 pure motor variants. Of the 43 patients diagnosed in the past, 36 patients (84%) were treated (intravenous immunoglobulins (IVIg) (29), prednisolone (2), subcutaneous immunoglobulins (SCIg) (2), dexamethasone (1), plasma-exchange (1) and IVIg with methylprednisolone (MP) (1)). The 35 recently diagnosed patients all received treatment (IVIg (12), dexamethasone (3), plasma-exchange (1) and 19 patients were treated in a pilot study with IVIg with methylprednisolone (MP)). The protocol has been evaluated and adjusted and will be shared with other researchers via the Inflammatory Neuropathy Consortium and IGOS Consortium. Our aim is to include at least 1000 CIDP patients worldwide with a minimum follow-up period of 2 years.

TRANSCRIPTIONAL AND TRANSLATIONAL PROFILING AND PRECLINICAL TESTING IN GARS/CMT2D MOUSE MODELS.

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Dominant mutations in glycyl tRNA synthetase (*GARS*) cause inherited axonal neuropathy (Charcot-Marie-Tooth type 2D). Mutations in the mouse *Gars* gene cause a similar phenotype, and represent valid disease models. We routinely use two mouse strains, one with a severe neuropathy, and one with a milder, later onset neuropathy. Using these mouse models, we are exploring the mechanisms through which *Gars* mutations cause peripheral axon degeneration. Efforts include ribosome tagging to isolate ribosome-associated mRNAs specifically from motor neurons, and non-canonical amino acid tagging to visualize and isolate newly synthesized proteins. Taking advantage of the anatomy of motor neurons, we are able to analyze cell bodies separately from peripheral axons in both of these approaches. In addition, we are using these mouse models for preclinical studies testing gene therapy approaches to treat CMT2D. Consistent with our previous genetic studies in mice, knockdown of the mutant transcript, while preserving sufficient levels of the wild type, is a very successful approach when administered before the onset of neuropathy. We are now testing this approach in mice after the onset of symptoms, and in mice carrying a mutant *Gars* allele associated with human disease. These studies are potentially translational, and also address mechanistic questions such as the timing and cell autonomy of the pathophysiology.

NEUROFASCIN ANTIBODIES IN AUTOIMMUNE, GENETIC AND IDIOPATHIC NEUROPATHIES.

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Autoantibodies to two isoforms of neurofascin (NF155 and NF186) have been reported in patients with Guillain-Barre syndrome (GBS) or chronic inflammatory demyelinating neuropathy (CIDP). It is not clear which of these responses reliably distinguish autoimmune neuropathies from other severe neuropathies, which responses are transient versus persistent, or which responses may target multiple isoforms of neurofascin. In addition, approximately 30% of neuropathy patients have no known cause, and it is unknown whether a subset of these patients may have autoantibodies to neurofascins. We have studied cohorts of patients with autoimmune neuropathy (n=150), genetic neuropathy (n=100), and idiopathic neuropathy (n=40) for IgG and IgM responses to Neurofascins. Neurofascin antibodies were found in 12 (8%) of patients with autoimmune neuropathy, and 3 (7.5%) idiopathic neuropathy patients, but only 1% (1 of 100) in patients with genetic neuropathy. Follow-up serum samples were available for 7 positive cases. Persistent responses were associated with chronic neuropathy while transient responses were seen in GBS or with remission of CIDP. Most patients had responses specific to either NF155 of NF186. However, a particularly severe, treatment-resistant form of CIDP, approaching a locked-in state, was seen in a patient with a unique response to all three isoforms of neurofascin (NF186, NF155, NF140). Treatment of this patient with rituximab resulted in clinical improvement and resolution of the neurofascin antibody response. In conclusion, autoantibodies to neurofascins distinguish autoimmune neuropathies from severe genetic neuropathies, but the clinical phenotype may depend on the persistence and isoform specificity of the immune response. Antibodies to the common domains shared by NF155 and NF186 may portend a severe but treatable neuropathy. A subset of idiopathic neuropathy patients may have an autoimmune mechanism.

RANDOMISED TRIAL OF PROGRESSIVE RESISTANCE EXERCISE FOR CHILDHOOD CHARCOT-MARIE-TOOTH DISEASE

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Exercise has undisputed benefits for human health and potentially as a treatment for neuromuscular disease. But there is also a risk of harm due to overwork weakness. We report the results of a 24-month randomised, double-blind, sham-controlled trial evaluating progressive resistance exercise of foot dorsiflexor muscles in pediatric CMT. Sixty patients (47 CMT1A, 1 CMT1E, 2 CMT1F, 1 CMT2A, 2 CMT4C, 4 CMTX1, 3 CMTX3) aged 6-17 years were randomly assigned to undergo 24-weeks (72 sessions) of moderate-intensity progressive resistance exercise or sham exercise. The primary endpoint was change in isometric dorsiflexion strength between groups assessed by hand-held dynamometry (expressed as a z-score based on age- and sex-matched normative reference values, positive values indicate an improvement in strength). The primary safety endpoint was change in muscle and fat volume of the muscles responsible for dorsiflexion by MRI between groups. Secondary outcomes were function (balance, long jump, 6-min walk test), walking ability (3D gait analysis), self-reported ankle instability, parent-reported quality of life (Physical Summary, Psychosocial Summary and Global Impression of Change scores), and adverse events. Fifty-five (92%) children completed the trial. Adherence was comparable between exercise (77%) and sham (81%) groups. While patients experienced muscle soreness during training in the exercise group, adverse events did not differ between groups. The mean z-score for dorsiflexion strength increased in the exercise group by 8% at 24-months (from -2.5±1.0 to -2.3±0.9) and decreased in the sham group by 24%, mirroring the natural history of CMT (from -2.1±0.7 to -2.6±1.2). Between-group ANCOVA-adjusted difference at 24-months was 0.6 (95%CI, 0.03 to 1.12; P=0.041). The mean scaled scores for MRI muscle volume and fat volume were comparable between groups at 24 months (P>0.05). The Global Impression of Change scores favoured the exercise group at 12-months (P=0.021) and 24-months (P=0.009). There was no other measurable effect of exercise. Pre-specified subgroup analyses according to age (6-11 years vs. 12-17 years) showed a larger treatment effect with exercise in adolescents. Targeted progressive resistance exercise was effective at halting progression of dorsiflexion weakness without detrimental effect on muscle morphology or other signs of overwork weakness in children with CMT.

INFLAMMATORY POLYRADICULOPATHY ASSOCIATED WITH SJOGREN'S SYNDROME

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A 51 years old female patient visited the hospital with weakness in both upper limbs from 9 months under the suspicion of motor neuron disease with the finding of extensive denervation changes on electromyography. Whole spine MRI showed ventral nerve rootlet enhancement in the C and T bundles. The EMG had confirmed active denervation changes in the muscles innervated by bilateral C5~C7 roots. The cerebrospinal fluid culture test showed a protein (CSF) elevation to 65 mg / dl. She got a steroid pulse therapy. She had the symptoms of dry mouth and dry eyes during the recent 2 years. A salivary gland scan test was performed for the possibility of Sjögren's syndrome, and as a result, absorption of the contrast agent in both parotid and submandibular glands was decreased. The Shammer test showed 8 mm on the right side and 7 mm on the left side. She was diagnosed of Sjögren's syndrome. After 2 weeks, overall strength improvement was observed, and bilateral shoulder abduction was improved to MRC grade 4 or higher. The follow-up spine MRI also showed that the initially seen ventral nerve root enhancement was disappeared. The case had visited the hospital with major symptoms of weakness and atrophy of the muscles, showing similar pattern to motor neuron disease, and was diagnosed as inflammatory polyradiculopathy and confirmed as primary SS during differential diagnosis. This case suggests that primary SS may induce inflammatory polyradiculopathy, which shows motor symptoms as major symptoms rather than sensory symptoms, and that a fast and accurate diagnosis is needed in terms that it can be treated with steroids and appropriate immune suppressive agents.

LOCAL INFUSION OF A LOW DOSE OF CURCUMIN IMPROVES NERVE REGENERATION AND FUNCTIONAL RECOVERY IN RATS SUBMITTED TO SCIATIC NERVE CRUSH INJURY

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Traumatic injuries to peripheral nerves are frequent. However, effective pharmacological treatments are lacking. Curcumin, a polyphenol found in rhizomes of *Curcuma longa*, has been shown to develop

antioxidant, anti-inflammatory, and neuroprotective properties. However, due to its poor hydrosolubility and its extensive metabolism, the use of large curcumin doses is required for therapeutic purpose. The aim of the present study was to investigate the effects of a local infusion of a low curcumin dose on nerve regeneration and functional recovery after sciatic nerve injury in rats. The experiments were conducted in 200 g SD male rats submitted to unilateral sciatic nerve crush at d0. Curcumin was solubilized in polyethylene glycol and continuously administered using osmotic pumps (0.2 mg/day until d35) with a catheter delivering the drug near the lesion site. Functional analyses using Von Frey, beam walking, static sciatic index (SSI) and grip strength tests were carried out at d0 (reference test) and every week after injury (d7, d14, d21, d28 and d35). In addition, an evoked electromyogram was performed at d0 and d35. After euthanasia (d35), nerve and muscle samples were collected and analyzed by light and electron microscopy. Functionally, a significant improvement of the mechanical sensitivity (+34%) was observed at d14 in the curcumin-treated group (n=12) *vs*. vehicle group (n=12). In curcumin-treated group, skillful walking and finger spacing of the ipsilateral paw (SSI) were fully restored respectively at d28 and d35 contrary to vehicle group. Furthermore, curcumin treatment improved the grip strength recovery (+24% at d35). The electrophysiological results indicated a full recovery of motor nerve conduction velocities (MNCV) after 35 days of curcumin treatment, while MNCV remained altered in vehicle group (79% of the MNCV at d0). Morphometric analysis of nerve sections using g-ratio showed an improvement in the thickness of the myelin sheath in curcumin treated animals (+13% *vs*. vehicle group). Histological investigation of gastrocnemius muscle indicated decreased neurogenic lesions in curcumin group. Proteomic analysis is currently under investigation to understand the mechanisms involved in curcumin effects. Our data could lead to the development of new therapeutic strategies in peripheral nerve regeneration using low doses of curcumin.

THE ASSOCIATION BEWTEEN THE METABOLIC SYNDROME AND NEUROLOGIC OUTCOMES IN A BARIATRIC SURGERY POPULATION

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Previous studies suggest that the metabolic syndrome (MetS) is associated with distal symmetrical polyneuropathy (DSP), and that diabetes, pre-diabetes, and obesity are the main metabolic drivers. The aim of this study is to investigate the association of MetS components with retinal and cognitive function in a bariatric surgery cohort prior to surgery. Patients were recruited from the Adult Bariatric Surgery Clinic at the University of Michigan and lean controls from a research website (no MetS components based on NCEP/ATPIII definition). Participants underwent extensive metabolic phenotyping including a glucose tolerance test and fasting lipid profile. DSP was defined using the Toronto consensus definition of probable clinical neuropathy. Retinal function was measured with frequency doubling technology perimetry (average mean deviation), and cognitive function with the NIH Toolbox (composite score). Univariate linear regression models were used to evaluate the association between MetS components and retinal and cognitive function. To date, we have recruited 45 bariatric surgery participants and 21 lean controls. In the bariatric population, the mean (SD) age was 47 (11.1) with 78% female compared with a mean age of 46.5 (11.3) with 76% female in the lean group. In the bariatric group, 35.6% had diabetes, 31.1% pre-diabetes, and 33.3% normoglycemia. The DSP prevalence was 0% in lean controls, 6.7% in normoglycemic, 7.1% in pre-diabetic, and 31.3% in diabetic bariatric participants ($p<0.001$ for trend). Retinal function was 0.01 (2.97), -0.21 (2.59), -3.36 (4.50), and -1.98 (4.27) ($p=0.02$ for trend), and cognitive function was 115.0 (12.0), 115.2 (20.0), 118.5 (20.9), 107.4 (14.4) ($p=0.36$ for trend) in these same groups for lean controls, normoglycemics, pre-diabetics and diabetics, respectfully. Pre-diabetes (-3.2, 95%CI: -5.97,-0.34) was the only MetS component associated with retinal function, and waist circumference was the only one associated with cognitive function (-1.76, 95%CI -3.4,-0.1). DSP and retinal function, but not cognitive function decline with worsening glycemic status. Similar to previous data for DSP, pre-diabetes and obesity are associated with retinal and cognitive function respectively. Interestingly, while clinical DSP is common in this population, clinical retinopathy and dementia are not, indicating that DSP may be the first metabolic complication in the morbidly obese.

PREVALENCE OF ANTI-NEUROFASCIN-155, ANTI-CONTACTIN-1 AND CONTACTIN-ASSOCIATED PROTEIN 1 ANTIBODIES IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: A SEROLOGICAL MULTICENTER STUDY IN ITALY

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Antibodies to neurofascin-155 (Nfasc155), contactin-1 (CNTN1) and contactin-associated protein (Caspr1) have been identified in 3-18% of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). However, their prevalence and associated clinical features in Italian CIDP patients are unknown. Serum samples from 150 patients fulfilling the ENFS/PNS criteria for definite CIDP were tested for anti-Nfasc155, anti-CNTN1 and anti-Caspr1 antibodies. Sera from additional 85 CIDP patients were tested for reactivity to anti-NFASC155 and anti-CNTN1. By ELISA, antibodies to Nfasc155 were found in 6 (3,5%) CIDP patients and to CNTN1 in 3 (1,3%). Anti-Nfasc155 and anti-CNTN1 antibody-positive cases were confirmed by CBA and were of IgG4 subclass in half of them. By CBA we identified additional 3/150 (2%) anti-Caspr1 seropositive patients, whose isotype is currently being tested. Sera of anti-Nfasc155 and anti-CNTN1 IgG4 seropositive patients and patients with anti-Caspr1 antibodies stained paranodes by indirect immunofluorescence on mouse teased nerve fibers. Of note, 35 seronegative patients for known antibodies showed reactivity against node and/or paranodes. Compared to other 35 seronegative CIPD patients, seropositive patients had more frequently subacute onset of the neuropathy and a younger age at onset, particularly for Nfasc155 or Caspr1 antibodies. Weakness was more severe and was often associated with proprioceptive loss, sensory ataxia and tremor. Neuropathic pain was not a feature of Caspr1-seropositive patients. Frequent findings were increased distal motor latencies and temporal dispersions on nerve conduction study and a higher protein level in CSF. Finally seropositive patients tended to have a higher disability and showed worst response to IVIg. Rituximab was effective in one patient with anti-Nfasc155 antibodies and two patients with anti-CNTN1 antibodies showed good and persistent recovery after Cyclophosphamide.
Prevalence of antibodies was 7% in Italian CIDP patients and their presence was associated with distinctive clinical features. Their determination, followed by characterization of IgG subclass in positive cases, has clear clinical impact, by helping to guide therapeutic choices. The reactivity against nodal and paranodal components in sera from patients without known antibodies suggests that other targets could play a role in the autoimmune response in CIDP and they still need to be identified.

CMT2 WITH PYRAMIDAL TRACT INVOLVEMENT DUE TO ARG329HIS MUTATION IN ALANYL-TRNA SYNTHETASE (AARS)

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Mutations in amynoacyl tRNA synthetases (ARSs), enzymes that catalyse the covalent attachment of amino acids to their cognate tRNA, are responsible for autosomal dominant CMT2, Intermediate CMT (CMT-I) and dHMN. We report the case of a male of Italian ancestry who first presented with bilateral ankle clonus at three months, followed by toe walking and ankle instability. The ankle clonus subsided during adolescence. In the third decade he developed progressive walking difficulties followed by distal sensory loss. Neurological examination at the age of 37 revealed a steppage gait, distal lower limb weakness, decreased pinprick to the ankles, and reduced vibration sensation at the knees. Reflexes were brisk in the upper limbs, reduced at the knees and absent at the ankles. Muscle tone was increased in the lower limbs and plantar responses were extensor. Nerve conduction studies revealed an axonal neuropathy. Brain and spinal cord MRI were normal. Sanger sequencing of *PMP22*, *GJB1*, *MPZ*, *GDAP* and *MFN2* were negative. SureSelect Focused Exome sequencing (Agilent Technologies, Santa Clara CA, USA) demonstrated a c.986G>A, p.Arg329His mutation in *AARS*.
The p.Arg329His mutation in *AARS* has previously been reported in 7 families with intermediate or axonal motor-sensory neuropathy, and in one case

was associated with sensory-neuronal deafness. CNS involvement has not previously been described with this mutation. Mutations in *AARS* have been associated with a range of phenotypes including CMTI, CMT2 and dHMN with variable age on onset ranging from 0 to 55 years (mean 24 years). Of note, the *AARS* p.Gly102Arg mutation has been reported in a family with CMT2 and pyramidal signs. This study provides further evidence that pyramidal tract involvement can be an early feature of CMT2N due to mutations in AARS, further expanding the spectrum of ARSs-associated phenotypes.

RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA RESULTS IN PAINFUL SMALL FIBRE NEUROPATHY

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Small fibres in the skin are vulnerable to damage in metabolic or toxic conditions such as diabetes mellitus or chemotherapy resulting in small fibre neuropathy and associated neuropathic pain (NP). Whether injury to the most distal portion of sensory small fibres due to a primary dermatological disorder can cause NP is still unclear. Recessive Dystrophic Epidermolysis Bullosa, (RDEB) is a rare condition in which mutations of proteins of the dermo-epidermal junction lead to cycles of blistering followed by regeneration of the skin. Damage is exclusive to the skin and mucous membranes, with no known direct compromise of the nervous system. It is increasingly recognised that most RDEB patients experience daily pain, the aetiology of which is unclear but may include inflammation (in the wounds), musculoskeletal (due to atrophy and retraction scars limiting movement) or NP. In this study we investigated the incidence of NP and examined the presence of nerve dysfunction in RDEB patients. Around three quarters of patients presented with pain of neuropathic characteristics which had a length dependent distribution. Quantitative sensory testing of the foot revealed striking impairments in thermal detection thresholds combined with an increased mechanical pain sensitivity and wind up ratio (temporal summation of noxious mechanical stimuli). Nerve conduction studies showed normal large fibre sensory and motor nerve conduction however skin biopsy showed a significant decrease in intraepidermal nerve fibre density. Autonomic nervous system testing revealed no abnormalities in heart rate and blood pressure variability however the sympathetic skin response of the foot was impaired and sweat gland innervation was reduced. We conclude that chronic cutaneous injury can lead to injury and dysfunction of the most distal part of small sensory fibres in a length dependant distribution resulting in disabling NP. These findings also support the use of neuropathic pain screening tools in these patients and treatment algorithms designed to target neuropathic pain.

ALTERED POTASSIUM CHANNEL DISTRIBUTION AND COMPOSITION IN MYELINATED AXONS SUPPRESSES HYPEREXCITABILITY FOLLOWING INJURY

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Neuropathic pain (NP) following peripheral nerve injury is associated with hyperexcitability in damaged myelinated sensory axons which begins to normalise over time. We investigated the composition and distribution of shaker type potassium channels (Kv1 channels) within the nodal complex of myelinated axons following injury. At the neuroma that forms after damage, expression of Kv1.1 and 1.2 (normally localised to the juxtaparanode) was markedly decreased. In contrast Kv1.4 and 1.6, which were hardly detectable in the naïve state, showed increased expression within juxtaparanodes and paranodes following injury, both in the rat and in humans. Within the dorsal root (a site remote from injury) we also noted a redistribution of Kv1 channels towards the paranode. Blockade of Kv1 channels with αDTX after injury reinstated hyperexcitability of A-fibre axons and enhanced mechanosensitivity. Changes in the molecular composition and distribution of axonal Kv1 channels, therefore represents a protective mechanism to suppress the hyperexcitability of myelinated sensory axons that follows nerve injury.

THE FRANCOPHONE ANTI-MAG COHORT: LESSONS LEARNED FROM THE ANALYSIS OF 202 PATIENTS.

(1) Camdessanché JP, (2) Petiot P, (1) Antoine JC, (3) Vial C, (4) Delmont E, (5) Viala K, (6) Magot A, (7) Cauquil C, (8) Zarea A, (9) Echaniz-Laguna A, (10) Iancu Ferfoglia R, (11) Guegen A, (12) Magy L, (13) Léger JM, (14) Kuntzer T, (15) Steck A, (1) Ferraud K, (1) Lacour A, (3) Svahn J, The Francophone anti-MAG cohort Group. (1) Department of Neurology, University Hospital of Saint-Etienne, 42055 Saint-Étienne Cedex 2 – France; (2) Department of Neurology, Croix-Rousse Hospital, Hospices Civils de Lyon, 103 grande rue de la Croix-Rousse, 69004 Lyon – France; (3) Electroneuromyography and Neuromuscular Department, GHE Neurologic Hospital, 69677 Lyon, Bron Cedex – France; (4) Department of Neurology, Timone Hospital, Marseille Teaching Hospital, Marseille – France; (5) Department of Neurophysiology and Neuropathology, AP-HP, GHU Pitié-Salpêtrière, Paris – France; (6) Neuromuscular Reference Center, CHU Nantes, 44093 Nantes Cedex 1; (7) Department of Neurology, Bicêtre Hospital, APHP, Le Kremlin Bicêtre, France; (8) Neuromuscular Competence Center, CHU Rouen, 73031 Rouen Cedex, France; (9) Reference Center of Neuromuscular Disorders, Neurology Department, Hautepierre Hospital, Strasbourg,

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Members of the Francophone anti-MAG cohort Group are listed in ‘‘Appendix’’.
Appendix: The Francophone anti-MAG cohort Group: Other members of the Francophone anti-MAG cohort Group who provided cases for the study are, in alphabetical order: David Adams, Hôpital Bicêtre; Sharam Attarian, CHU de Marseille; Anne-Laure Bedat-Millet, CHU de Rouen; Françoise Bouhour, CHU de Lyon; Célia Boutte, CHU de Grenoble; Guy Chauplannaz, CHU de Lyon; Raquel Costa, Hôpital Pitié-Salpêtrière; Perrine Devic, CHU de Lyon; Chantal Grand, CHU de Lyon; Guillemette Jousserand, CHU de Lyon; Timothée Lenglet, Hôpital Pitié-Salpêtrière; Pierre Lozeron, Hôpital Bicêtre; Thierry Maisonobe, Hôpital Pitié-Salpêtrière; Cristina Muntean, Hôpital Pitié-Salpêtrière; Yann Pereon, CHU de Nantes; Jean Pouget, CHU de Marseille.

Polyneuropathy with anti-MAG IgM antibodies is classically progressive, predominantly sensory, and distal with ataxia and sometimes postural-intention tremor.
We assessed clinical, biological, electrophysiological, and histopathological features in patients with IgM gammopathy and anti-MAG antibody titres higher than 1000 BTU. We focused on characteristics of patients according to the anti-MAG antibody titres at diagnosis.
We retrospectively and prospectively analysed standardized report forms of 202 patients from fourteen French-speaking neuromuscular centres.
Mean age at onset was 62.6 years (range 25-91.4). Mean time between symptoms onset and last follow-up was 8.4 years (0.3-33.3). About 33.2 % of patients presented with a “variant” clinical phenotype independently of anti-MAG titres (< or ≥ 10 000 BTU). This included acute or chronic sensorimotor polyradiculoneuropathies, paucisymptomatic sensory polyneuropathy and multifocal neuropathy. At the most severe disease stage, 22.4% of patients were significantly disabled. Anti-MAG antibody titres at diagnosis were low (< 10 000 BTU), medium (10 000-70 000) or high (≥ 70 000) in respectively 11, 51 and 38 % of patients. Patients presented with MGUS or Waldenström's macroglobulinemia in respectively 68 % and 29 % of cases. Sixteen percent of patients did not meet the electrodiagnostic criteria of definite demyelinating neuropathy, independently of anti-MAG titres (< or ≥ 10 000 BTU). Nerve biopsy, performed in nineteen patients, provided support to the diagnosis of anti-MAG neuropathy in some particular issues (low titres of anti-MAG, unusual clinical or electrophysiological phenotype). We assessed the degree of probability (probable, possible or uncertain) that patient neuropathies are directly related to anti-MAG antibodies, according to anti-MAG titre, electrophysiological data and nerve biopsy characteristics if available. It appears uncertain in 5 patients with low anti-MAG titres (2.5 % of the whole population).
The clinical phenotype didn’t appear to be different according to anti-MAG antibody titre. Many of the patients with low anti-MAG titres presented “genuine” anti-MAG neuropathy as demonstrated by EDX studies, clinical presentation and sometimes nerve biopsies. For a small proportion of these patients, a direct relation between neuropathy and anti-MAG antibodies is uncertain due to atypical clinical presentation, axonal neuropathy pattern or nerve biopsies, and positivity of antigangliosides antibodies.

THE FRANCOPHONE ANTI-MAG COHORT: ANALYSIS OF THERAPEUTIC MANAGEMENT IN 202 PATIENTS.

(1) Camdessanché JP, (2) Petiot P, (1) Antoine JC, (3) Vial C, (4) Delmont E, (5) Viala K, (6) Magot A, (7) Cauquil C, (8) Zarea A, (9) Echaniz-Laguna A, (10) Iancu Ferfoglia R, (11) Guegen A, (12) Magy L, (13) Léger JM, (14) Kuntzer T, (15) Steck A, (1) Ferraud K, (1) Lacour A, (3) Svahn J, The Francophone anti-MAG cohort Group. (1) Department of Neurology, University Hospital of Saint-Etienne, 42055 Saint-Étienne Cedex 2 – France
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Muscle Unit, Department of Clinical Neurosciences, Lausanne University Hospital (CHUV), Lausanne, Switzerland.; (15) Department of Neurology, Basel University Hospital, Basel, Switzerland.
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We assessed therapeutic management, response to immunotherapies and adverse events in a cohort of 202 patients presenting with IgM gammopathy and anti-MAG antibody titres higher than 1000 BTU.
We retrospectively and prospectively analysed standardized report forms of 202 patients from 14 French speaking neuromuscular centres.
Mean age at onset was 62.6 years (range 25-91.4). Mean time between symptoms onset to diagnosis and last follow-up were respectively 3.1 (0-30) and 8.4 years (0.3-33.3). Anti-MAG antibody titres at diagnosis were low (< 10 000 BTU), medium (10 000-70 000) or high (≥ 70 000) in 11, 51 and 38 % of patients. Patients presented with MGUS or Waldenström's macroglobulinemia in respectively 68 % and 29 % of cases.
Seventy eight percent (n = 158) of patients received immunotherapies. Transient response to IVIg or plasma exchanges at six month was observed in less than 30 and 20% of patients respectively. Chemoimmunotherapies and rituximab were more frequently administered in the group of patients with malignant hemopathies (n = 65) compared to MGUS (n = 137) (mean lines of therapy = 1.2, range 0-4, SD 0.7 versus 0.85, range 0-3, SD 0.85, p = 0.002). More than 45% of patients (n = 92) received rituximab monotherapy. Clinical worsening, mostly transient and reversible, was observed in 11/92 patients after rituximab. Clinical response to rituximab at 6 months and/or during 7-12 months follow-up period was observed in 31.5% of patients, and correlated with anti-MAG titre ≥ 10 000 BTU (30/31 responder versus 50/61 non-responder patients, p = 0.05). At 7-12 months follow-up, responder patients presented shorter symptom duration compared to non-responders, though not significant after logistic regression (3.6 years, range 0.13-16.23, SD 3.7 in 29 responder patients versus 5.1 years, range 0.13-17.6, SD 4.2, in 63 non responder patients, p = 0.1). In some cases, electrodiagnostic studies were recorded during rituximab treatment follow-up and showed in responder patients a clear improvement of motor conduction velocities. These data may support another clinical trial to study benefice of rituximab in anti-MAG neuropathies early in the disease. It raises issues about the value of incorporating electrodiagnostic parameters as end-points.

N-METHYL-D-ASPARTATE RECEPTOR (NMDA-R) ACTIVATED CELL-SIGNALING IN RESPONSE TO GLUTAMATE IN SCHWANN CELLS

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Schwann cells (SCs) are essential for axon integrity and myelination in the uninjured PNS. After PNS injury, SCs function as “first responders”, undergoing phenotypic re-programming and orchestrating many processes that lead to functional nerve repair. Receptors in SCs that contribute to SC repair programs remain incompletely understood. We identified a member of the ionotropic glutamate receptor (IGR) family, N-methyl-D-aspartate receptor (NMDA-R), in SCs that is upregulated after nerve injury and acts as a co-receptor with LDL-receptor related protein (LRP1). LRP1 is a well-known regulator of the SC response to PNS injury. Herein, we used PCR to profile IGR expression in cultured rat SCs. Obligate receptor subunits required for assembly of NMDA-Rs, AMPA-Rs, and Kainate Receptors were identified. Treatment of rat SCs with 40-100 microM glutamate or 0.5-1.0 microM NMDA robustly activated Akt and ERK1/2. The response was transient and bimodal; glutamate concentrations greater than 250 microM failed to activate cell-signaling. Phosphoprotein profiling demonstrated other cell-signaling and transcription factors regulated by glutamate in rat and human SCs, including p70 S6-kinase, glycogen synthase kinase-3, ribosomal S6 kinase, c-Jun, and CREB. Activation of cell-signaling by glutamate in SCs was blocked by eliminating calcium from the medium, by the selective NMDA-R antagonist, MK801, and by genetic silencing expression of the obligate NMDA-R NR1 subunit. Phosphoinositide 3-kinase/PI3K functioned as an essential upstream activator of both Akt and ERK1/2 in glutamate-treated SCs. By activating PI3K and ERK1/2, glutamate promoted SC migration. Glutamate (200 microM) or NMDA (20 microM) injected into crush-injured sciatic nerves robustly activated p-ERK1/2 in both myelinating and non-myelinating SCs *in vivo*. These results identify IGRs as potentially important cell-signaling receptors in SCs that may promote axon-glial interactions. Understanding the function of SC NMDA-R is important given current efforts to develop NMDA-R-targeting drugs for patients with pain, depression, and Alzheimer’s Disease. While frequently overlooked in a therapeutic context, SCs are extremely important in the pathogenesis of chronic neuropathic pain. If these drugs modulate the activity

of SC NMDA-R and SC physiology, the response to PNS injury may be altered and the possibility that neuropathic pain develops increased.

MUTATION SPECTRUM IN A TURKISH CHARCOT-MARIE-TOOTH DISEASE COHORT

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Charcot-Marie-Tooth (CMT) disease is a group of inherited peripheral neuropathies affecting one in 2500 individuals worldwide. The disease presents both clinical and genetic heterogeneity. So far, mutations in 80 genes and 10 loci are associated with CMT with autosomal dominant, autosomal recessive, X-linked and mitochondrial inheritance. Despite the advances in genetic testing, approximately 35% of all CMT patients worldwide remain without a molecular diagnosis. We have investigated 93 unrelated CMT patients of Turkish descent, in all of which PMP22 duplication has been excluded previously. We used Multiplex Amplification of Specific Targets for Resequencing (MASTR) assay to sequence exonic regions of 28 common CMT genes. Recurrent mutations were identified in 14 cases in MFN2, GJB1, MPZ and HINT1 genes. We have also identified novel variants in 11 cases in MFN2, PMP22, GARS, AARS, IGHMBP2 and GDAP1 genes, all of which are very rare or not present in the variation databases and are predicted to be pathogenic by in silico tools. Familial segregation analyses are ongoing for novel variations. MFN2 and GJB1 genes were the most commonly mutated causative genes in this cohort. Cases without molecular diagnosis after the MASTR testing are candidates for further analyses such as whole exome sequencing or whole genome sequencing. Outcomes of the current study and our previous experience with Turkish CMT patients suggest a high genetic heterogeneity. Our insight is that different genetic strategies or larger panels are essential to determine the causes underlying CMT especially in regions where rare recessive types of the disease can be observed due to high frequency of consanguineous marriages.

TOTAL COMPOUND MUSCLE ACTION POTENTIAL DURATION: A NEW USEFUL ELECTROPHYSIOLOGICAL MEASURE FOR EARLY GBS DIAGNOSIS

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Several efforts have been made to elaborate new electrophysiological criteria for early diagnosis of Guillain-Barré Syndrome (GBS) and to differentiate demyelinating (AIDP) from axonal (AMAN/AMSAN) forms. The aims were to verify the diagnostic power of total CMAP (TCMAP) duration, firstly applied in GBS field. This parameter was compared with commonly used neurophysiological measures, including negative phase CMAP duration (NCMAP), and was added to modified Rajabally criteria. We reviewed the clinical and electrophysiological data of 38 patients with GBS (level 1 or 2 of Brighton clinical criteria). Each patient underwent at least two neurophysiological studies, the first within 2 weeks, the second between 3 and 7 weeks from symptom onset. At least four motor and three sensory nerve conduction studies were recorded for each test. Regarding early diagnosis, the binary logistic regression model with multiple variables, including NCMAP duration, showed that the 3 features of predictive model presenting greater significance ($p < 0.1$) were TCMAP duration, Sural Sparing and A-waves. Among these, TCMAP duration showed greater significance ($p = 0.002$). The TCMAP was diffusely prolonged in AIDP compared to AMAN/AMSAN, already in first examination and confirmed in the second one. ROC analysis for TCMAP duration in AIDP vs. AMAN/AMSAN showed: cut-off 15.7 ms, AUC 0.89, PPV 91.3%. We propose the TCMAP duration as a new useful electrophysiological measure for early diagnosis of "generic" GBS and for early differentiation between AIDP and AMAN/AMSAN. Moreover, the prolongation of TCMAP, the presence of A-waves and Sural Sparing represent a strongly diagnostic predictive triad of AIDP.

NOVEL PHE210LEO MISSENSE MUTATION IN *AIFM1* GENE IS ASSOCIATED WITH AN AXONAL POLYNEUROPATHY

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AIFM1 (apoptosis-inducing factor, mitochondrion-associated-1) has captured great attention from biomedical researchers due its critical role in the regulation of cell apoptosis. This flavoprotein is typically located in the mitochondrial intermembrane space where it is associated with respiratory chain complex-I. Upon a cell-death insult, AIFM1 is cleaved into a 57Kd protein that is released into the cytosol. The 57Kd peptide may enter the nucleus to trigger chromosome condensation and fragmentation, initiating a caspase-independent pathway of apoptosis. However, this nuclear translocation may be blocked by cytosolic Heat-Shock Protein-70 (HSP70) that binds with the FAD domain (aa 150 – 228) of AIFM1. Mutations in *AIFM1* gene have resulted in several clinical phenotypes, including a family with CMTX4 (Glu493Val). Clinical deficits in these patients usually involve multiple organs. In this study however, we identified a family with a novel missense mutation (Phe210Leu) in *AIFM1* that developed a late-onset sensory motor axonal polyneuropathy by nerve conduction criteria. The proband and affected siblings exhibited distal muscle weakness and atrophy with normal cognitive and cranial nerve functions. There was no obvious

phenotype from other organs. Interestingly, this Phe210Leu mutation affects a highly conserved amino acid at the center of the FAD domain. We hypothesize that this mutation impairs the binding between AIFM1 and HSP70, leading to an enhancement of cell-death signaling. This family therefore provides a unique opportunity to explore how altered apoptotic signaling affects peripheral nerve system. Supported by grants from NINDS (R01NS066927) and the National Center for Advancing Translational Sciences (UL1TR000445).

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY ASSOCIATED WITH LYMPHOMA : MONOCENTRIC STUDY.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) can be the key symptom leading to diagnosis of associated lymphoma. Patients with diagnosis of CIDP according to EFNS/PNS criteria associated with B cell lymphoproliferative disorders (BLD), in one center, between November 2013 and November 2016 were included. Demographical, clinical, nerve conduction, immunological, histological data and response to treatment were recorded retrospectively. Eight patients (5 men), median age 70yo [53-77] were included. Onset of polyradiculoneuropathy was either chronic (n=6) or acute (n=2). Neurological condition led to diagnosis of BLD in all but one case, because of onset (n=4) or worsening of neuropathy (n=3). Clinical presentation was that of CIDP in 5 patients or pseudo-CANOMAD in 2 and plexopathy in one. Lymphoma type was: lymphoplasmacytic (n=3), diffuse large B cell (n=2), small lymphocytic (n=1), marginal zone (n=1), unclassified small B cell (n=1). Only 2 patients presented with lymphadenopathies. BLD was diagnosed in all 8 patients on myelogram or bone marrow biopsy, performed because of cytopenia (n=2), atypical (n=3) or severe (n=3) neuropathy. Monoclonal gammapathy was identified in 5/8 patients (IgM n=4, IgG n=1). Neuromuscular biopsy was performed in 6 patients and disclosed endoneural infiltration in 2. Anti-neuronal or antigangliosides antibodies were positive in 5 patients. None of the patients presented a systemic autoimmune disease, hemolytic anemia associated with BLD (n=2). Immunomodulating treatment was administered in all patients (IVIG n=7, plasma exchange n=3, steroids n=3) and immunosuppressants (n=1). Immunochemotherapy for lymphoma was initiated because of lymphoma type or severity in 3 cases, in 5 cases because of the associated neuropathy. Median follow-up was of 8 months [1-24] after treatment initiation. Four out of 5 patients treated within 3 months of neurological onset improved as well as one out of 3 patients whose preexisting neurological condition had worsened. Two patients presented neurological relapse during progression of lymphoma. Two patients died. Unusual presentation of CIDP –*i.e.*, rapid progression or treatment failure - should lead to further testing for associated lymphoma. Because general symptoms and lymphadenopathy often lack, diagnosis requires analysis of bone marrow with lymphocyte phenotyping. Early treatment with immunochemotherapy was associated with better prognosis in our series.

CARDIAC SCINTIGRAPHY IS A USEFUL TOOL FOR THE DIAGNOSIS, PROGNOSIS AND PRE-SYMPTOMATIC EARLY DETECTION OF FAMILIAL AMYLOIDOSIS ASSOCIATED NEUROPATHIES

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Familiar amyloidosis is a group of diseases characterized by tissue deposition of amyloid fibrils. There are three main types of familiar amyloidosis: transthyretin (TTR), apolipoprotein A1 and gelsolin. Cardiac involvement is a leading cause of morbidity and mortality; one new described mutation strongly related with isolated cardiac amyloidosis is the TTR Val122Ile. The discovery of tests that allow early diagnosis of cardiac involvement in amyloidosis and to infer about the etiology of the disease is of major importance. In a cohort of patients with different types of familiar TTR amyloidosis, we aimed to assess the role of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) in detecting myocardial amyloid infiltration. We enrolled four patients diagnosed with late familiar amyloidosis, which mutations were documented at deoxyribonucleic acid analysis: three patients with TTR Val30Met mutation and one patient with TTR Val122Ile mutation. Three patients were asymptomatic for cardiac involvement and one patient (Val122Ile mutation) had a previous diagnosis of heart failure. Myocardial uptake of 99mTc-DPD scintigraphy was semiquantitatively and visually assessed at five minutes and three hours.The uptake of 99mTc-DPD highly demonstrated amyloid in cardiac area in two out the three cases of TTR Val30Met and in TTR Val122Ile. TTR Val122Ile case presented the highest uptake due to the exclusive deposition of amyloid in cardiac area resulting in severe heart failure.

In hereditary transthyretin-related amyloidosis, including the mutations TTR Val30Met and Val122Ile, 99mTc-DPD cardiac scintigraphy can identify infiltration even in asymptomatic individuals, allowing an early diagnosis of cardiac compromise in this group of diseases. We can consider that this non-invasive test would be a tool with potential importance in the diagnosis, prognosis and pre-symptomatic early detection of cardiac amyloidosis, giving emphasis on its applicability in familial forms of amyloidosis.

MILD ERK/MAPK ACTIVATION IN ADULT SCHWANN CELLS NEGATIVELY AFFECTS AXON SURVIVAL, MYELIN STABILITY AND SMALL FIBRES REINNERVATION AFTER NERVE INJURY.

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ERK/MAPK pathway has a critical role in PNS development since its involvement in many physiological processes. Sustained ERK1/2 MAPK activation in Schwann cells enhances myelin growth during development and overcomes signals ending myelination leading to a continuous myelin production. However, strong activation of ERK has also been shown to cause Schwann cells dedifferentiation and demyelination *in vivo*. Our aim was to investigate whether a mild activation of this signalling pathway in adult Schwann cells (SCs), by expression of gain of function Mek1DD allele, could have a beneficial role in remyelination and regeneration after injury. Erk/MAPK activation in adult SCs in PLPCreER^{T2};Mek1DD mutant mice, did not affect myelination during development. Following sciatic nerve injury, Wallerian degeneration was enhanced in mutants pushing towards a dedifferentiation stage of SCs as previously described. However, MAPK activation was detrimental during regeneration with a delay in functional recovery and a negative impact in both myelinated and non-myelinated fibres compared to controls. One month after injury the total number of axons in mutant sciatic nerves was half of the controls. Although no differences in g-ratio have been found in the two groups, mutants presented a higher number of myelinated axons showing myelin disruption with start of myelin decompaction, lack of Cajal bands, abundant SC processes surrounding axons and a shorter SC elongation, as seen by decreased internodal distance. In addition, we found a negative effect of MAPK activation also in small diameter axons with the presence of abnormal Remak bundle structures, reduced number of c-fibres/Remak bundle and a significant decrease in intra epidermal nerve fibres density in the skin.
We concluded that mild MAPK activation has a different role in development and remyelination where negatively affects axon survival, myelin stability, Remak bundle formation and small fibres regeneration.

NEPRILYSIN IS NOT INVOLVED IN REGENERATION AND RE-MYELINATION AFTER NERVE INJURY.

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Neprilysin (NEP) is an endopeptidase which has been of interest due to its potential role in neurodegeneration and pain as a consequence of its ability to degrade amyloid and substance-P respectively. NEP expression is not limited to CNS and it has been reported to be expressed in Schwann cells, nodes and Schmidt-Lanterman incisures. Our interest in this gene was related to recent findings that have associated homozygous and heterozygous NEP mutations with Charcot-Marie-Tooth type-2. In old mice lacking NEP subtle morphological changes have been reported.
Our aim was to determine whether NEP expression was modulated by nerve injury and to investigate its role in axon regeneration and re-myelination.
We find that NEP gene expression was decreased after nerve crush and furthermore was dependent on the growth factor (and pro-myelin signal) Neuregulin-1. In control mice NEP expression was transiently reduced and returned to baseline at day 28 after injury, in Neuregulin-1 knock-out (KO) mice, in which re-myelination was impaired, the expression was still decreased at day 28. In assessing behavioural measures of locomotor and sensory function one month after sciatic nerve crush, NEP KO mice showed a functional regeneration comparable to WT, as seen by sciatic functional index measurement, beam and toe spreading tests. The only significant difference we observed between WT and KO was in the sensorial test, showing KO mice recovering faster in the pinch test by 13 days after crush. The results for all the tests at baseline did not differ between the two groups. Detailed histological analysis of nerve repair was undertaken using electron microscopy. There was no difference between WT and KO in total axon number, g-ratio, axon diameters and other myelin features one month post crush.
In summary, although NEP expression is regulated by nerve injury in a Neuregulin-1 dependent fashion this endopeptidase is dispensable for axon regeneration and re-myelination after nerve injury in the rodent.

SENSORY AXONAL DYSFUNCTION IN THE PAINFUL DIABETIC POLYNEUROPATHY

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Diabetes neuropathy is a common complication of diabetes, and neuropathic pain has a detrimental impact on quality of life. This study investigated sensory nerve excitability properties to elucidate the axonal changes of diabetic neuropathy. A total of 95 diabetes patients (93 type II, and 2 type I) were enrolled in this study. Clinical assessment, nerve conduction studies, and nerve excitability testing data were analyzed to determine axonal dysfunction in diabetic neuropathy. Among those patients, seventeen subjects had complained of spontaneous painful sensation over feet or hands (painful cohort), and seventy-eight patients had no sensory symptoms or decreased the sensation over foot (non-painful cohort). Sensory nerve excitability of the painful

cohort showed reduced late subexcitability (p=0.01), increased superexcitability (P=0.03) in compared to the non-painful cohort. There is no difference in disease duration, blood glucose levels (HbA1c) between these two cohorts. These findings suggested the possible pathogenesis of painful sensory axons might be hyperpolarized or slow potassium channels dysfunction. These insights our further understanding of painful diabetic neuropathy, and may provide a basis for neuroprotective or therapeutic approaches for painful polyneuropathy.

MRI OF THE BRACHIAL PLEXUS AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: ASSESSMENT OF DTI-DERIVED MEASUREMENTS AT 3.0-T

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The main purpose of this study was to assess the clinical feasibility of diffusion tensor imaging (DTI) for the diagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).
Between March 2013 and December 2015, we prospectively enrolled 15 patients with definite CIDP according to the EFNS 2010 criteria and two control groups: 15 healthy volunteers matched on age and sex and 15 patients with CMT-1A. Using a 3-T magnetic resonance imaging scanner, we obtained DTI scans of brachial plexus of these 3 groups and prepared Fractional Anisotropy (FA) maps, and compared these values between groups. ADC values and cervical nerve roots diameters on STIR sequences were evaluated too. Two neuroradiologists, blinded to clinical informations, reviewed MRI studies independently. In all patients with CIDP, we also performed clinical evaluation and electroneuromyography.
Significantly decreased FA values ($p<0.001$) and increased ADC values were observed in CIDP patients compared with healthy subjects. There is no significant difference between CIDP and CMT group. Inter-observer concordance was excellent for FA values (ρc=0.891; $p<0.001$) and moderate for ADC values (ρc=0.537; $p<0.001$) and cervical nerve root diameters (ρc=0.495; $p<0.001$). There is a significant correlation between FA and disease duration ($r = -0.5$, $p <0.05$), inclusion MRC score ($r = 0.56$, $p <0.05$) and between FA mesured on C7C8 and INCAT score at inclusion ($r = -0.53$, $p <0.05$). No significant correlation is observed between FA and electrophysiological indices. Compared with healthy subjects, cervical nerve root diameters were significantly increased ($p<0.001$) in patients with CMT and CIDP. Contrary to FA values, moderate level of concordance was found between inter-observers measurements of diameters (CClin = 0.495).
Our preliminary data prove the clinical feasibility and reproductibility of DTI for the evaluation of plexus and cervical nerve roots in patients with CIDP.

DISRUPTION OF BLOOD-NERVE BARRIER AT ENTRAPMENT SITES RATHER THAN NERVE ENDINGS IS THE LIKELY CAUSE OF SURAL-SPARING PATTERN IN GUILLAIN-BARRE SYNDROME

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The sural-sparing pattern of the sensory nerve action potentials (SNAP) of Guillain-Barré syndrome (GBS) has been attributed to greater immunological injury of the blood-nerve barrier at its most vulnerable regions. We asked if entrapment sites, such as median nerve at the wrist, are more predisposed than the distal nerve endings to such injury. We compared the median SNAP with radial SNAP measured antidromically at digit 1 in GBS patients whose nerve conduction study showed the sural-sparing pattern. The terminal nerves at digit 1 are of similar length, but those of median nerve are prone to compression, often subclinically, at the carpal tunnel while those of radial nerve are not. We defined the sural-sparing pattern as a greater decrease in median and or ulnar SNAP than that of the sural, compared to age and height-matched normal controls. A total of 35 GBS and Miller Fisher patients from our institution's database were studied. 15 patients had the sural-sparing pattern, of whom 1 had pre-existing carpal tunnel syndrome. Of the remaining 14 patients with sural-sparing, 11 had abnormal median SNAP at digit 1, while 3 had both abnormal median and radial SNAPs at digit 1. None had isolated abnormality of the radial digit 1 SNAP. Among the 3 cases that had abnormal median and radial SNAPs at digit 1, the mean percentage decrease when compared to age and height matched norms was greater in median nerve compared to radial nerve (97% and 75% respectively). Of the 20 patients without sural-sparing pattern, 18 had normal SNAPs; 1 patient had inexcitable sensory nerves while the other had a length-dependent decrease in SNAP. In the latter patient, unlike those with sural-sparing, there was no differential decrease of median SNAP over radial SNAP at digit 1. Our findings suggest that the disruption of blood nerve barrier at entrapment sites rather than the distal nerve endings may underlie the pathophysiology of the sural-sparing pattern seen in GBS.

Ca(2+)-DEPENDENT ANTI-GQ1B ANTIBODY IN FISHER SYNDROME: DETECTION AND INSIGHT INTO THE MOLECULAR MECHANISM.

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Serum IgG anti-GQ1b antibody is the most specific biomarker for Fisher syndrome and its related disorders (FS-RD), but approximately 10-30% of the patients are seronegative for it in conventional assays (GQ1b-seronegative). Some molecules need Ca^{2+} cation to interact with their ligands, and antibodies with such a property (Ca^{2+}-dependent antibodies) are reported. We have found that such a Ca^{2+}-dependency is also present in IgG anti-GQ1b antibody, and majority of GQ1b-seronegative patients with FS-RD have this type of antibodies. In 66 patients with final clinical diagnoses as FS-RD (Fisher syndrome, Guillain-Barré syndrome with ophthalmoplegia, Bickerstaff brainstem encephalitis, and acute ophthalmoplegia), 55 were seropositive for IgG antibodies against GQ1b-related antigens (isolated GQ1b in 53, and GQ1b-conatinig complexes in two) in conventional ELISA using phosphate-buffered saline. In the remaining 11 patients, eight (73%) turned positive for IgG antibody against GQ1b-related antigens (isolated GQ1b in seven and GQ1b-conatinig complexes in one) in ELISA using Ca^{2+}-added Tris-buffered saline. The reaction strengths increased depending on Ca^{2+} concentration, and reached to nearly maximum level in the physiological concentration. All the patients with the Ca^{2+}-dependent antibodies were also positive for IgG antibody against GT1a-related antigens, suggesting that the terminal disialo residue common to both the gangliosides would be important as an epitope also for the Ca^{2+}-dependent antibodies. In the 55 patients with Ca^{2+}-non-dependent antibodies, only two showed increased titers of IgG anti-GQ1b antibody by adding Ca^{2+}, and 31 showed significantly decreased titers. This difference in the effect of Ca^{2+}-addition between Ca^{2+}-dependent and Ca^{2+}-non-dependent antibodies suggests that Ca^{2+} would not be just an enhancer of the antigen-antibody reaction. There are four single bonds between the two pyranose rings in the terminal disialo, and those rotatable bonds make it possible for the disialo structure to take various conformations. A molecular model shows that the distance between two minus-charged carboxy groups in the disialo could vary from nearly zero to approximately 1,000 pm and that the disialo would take specific conformations, if divalent Ca^{2+} cation, which size is approximately 400 pm in diameter, interacts with these two minus-charged groups. The Ca^{2+}-dependent antibodies might recognize such particular conformations of GQ1b.

AMINOACYL tRNA SYNTHETASE GENE MUTATIONS INCLUDING GARS, MARS AND YARS GENES IN KOREAN PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE

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Charcot-Marie-Tooth disease (CMT) is a genetically and clinically heterogeneous disorder with variable inheritance modes. It is characterized by loss of muscle tissue and touch sensation, predominantly in the feet and legs but also in the hands and arms in the advanced stages of disease. As several molecules have been reported to have therapeutic effects on CMT, depending on the underlying genetic causes, exact genetic diagnostics have become important for executing personalized therapy. Aminoacyl-tRNA synthetase (ARSs) genes encode enzymes responsible for charging tRNA with corresponding amino acids. ARSs are ubiquitously expressed, essential enzymes responsible for performing the first step of protein synthesis. Specifically, ARSs attach amino acids to their cognate tRNA molecules in the cytoplasm and mitochondria. Recent studies have demonstrated that mutations in genes encoding ARSs can result in neurodegeneration, raising many questions about the role of these enzymes in neuronal function. Mutations in six cytoplasmic ARS genes have been reported as the cause of CMT. This study was performed the whole exome sequencing to identify genetic defects in 392 Korean CMT patients from 280 unrelated families. Variants were sorted with CMT gene list that includes almost 80 genes were related CMT neuropathy, and additionally sorted WES data as ARS genes. Capillary sequencing for family members and more than 500 controls revealed five novel mutations, c.598G>A (p.D200N), c.794C>T (p.S265F), and c.1007C>A (p.P336H) in *GARS*; c.2398C>A (p.P800T) in *MARS*; 241_242GA>AT (p.D81I) in *YARS* gene in each family. The mutation sites were well conserved between different species and each mutation were located in the well-conserved catalytic domain or between two catalytic domains or anticodon-binding domain. *In silico* analysis predicted all mutations may affect protein function. Clinical features were similar to those reported in other countries, but differed in terms of age at onset and degree of disability. We believe that those novel ARS mutations are the underlying causes of the each family.

SPINOBULBAR MUSCULAR ATROPHY COMBINED WITH CHARCOT-MARIE-TOOTH DISEASE: “DOUBLE TROUBLE” IN NEUROMUSCULAR DISORDERS

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A 64-year-old man presented with a 26-year-history of weakness in biltearal upper limbs. He was complaining of intermittent fasciculation of upper and lower limbs with gradually worsening of paresthesia for 20 years. Dysphagia and dysarthria were also

presented 5 years ago. There was no patient affected muscle weakness and bulbar symptoms in his family members. In neurological examination, the patient had weakness in biltereal upper and lower limbs (MRC grade 3) and prominent distal sensory loss were combined in length dependant pattern. Deep tendon reflexes were absent on bilataral biceps and knee joints. In nerve conduction study, there was consistent with demyelinating sensorimotor polyneuropathy. Molecular diagnostic analyses those spinobulbar muscular atrophy (SBMA) and mutation related to peripheral myelin protein 22 (PMP22) gene were performed and confirmed expansion of expansion of a polymorphic CAG in androgen-receptor (AR) gene and deletion of PMP22 gene. SMBA, also known as Kennedy disease, is an adult-onset, X-linked recessive trinucleotide, polyglutamine (poly-G) disorder caused by expansion of a polymorphic CAG tandem-repeat in exon 1 of AR gene on chromosome Xq11-12. Charcot-Marie-Tooth disease (CMT) is the most common hereditary neuropathies and CMT cases with motor conduction velocities(MCVs) of upper limb below 38 m/s are defined as demyelinating (CMT1) and those with MCVs above 38 m/s are defined as axonal (CMT2). Most families with CMT1 linked to duplication of PMP22 gene on the short arm of chromosome 17(17p11.2), called CMT1A. The reciprocal deletion of PMP22 gene is a responsible genetic defect in 70% of hereditary neuropathy with liability to pressure palsy (HNPP). These “classical” phenotypes of CMT1A and HNPP have been considered which are determined by different mutation mechanism of the same gene. However, an overlap of CMT1A and HNPP due to PMP22 gene deletion was reported that suggestion the phenotype of hereditary neuropathies may differ variably. Herein, we report a patient who simultaneously presented clinical and electrophysiologic features of SMBA and CMT1A with genetical confirmation of CAG expasion and deletion of PMP22 gene.

A COMBINATION OF THREE REPURPOSED DRUGS (PXT3003) SYNERGISTICALLY INCREASES MYELINATION IN CO-CULTURES OF SCHWANN CELLS AND NEURONS DERIVED FROM CMT1A RATS.

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Charcot-Marie-Tooth type 1A disease (CMT1A) is an inherited peripheral neuropathy stemming from overexpression of PMP22 protein in Schwann cells due to the duplication of the PMP22 gene. This leads to abnormal Schwann cell differentiation and dysmyelination, eventually leading to axonal loss and muscle wasting. No approved treatment is currently available for CMT1A. We conducted a systems biology level analysis of the signaling network putatively underlying the processes driving CMT1A pathology. Based upon this, we identified and tested three repurposed drugs – baclofen, naltrexone and sorbitol – alone and in combination to determine their ability to rescue aberrant myelination in cultures derived from CMT1A transgenic rats overexpressing PMP22 gene. To this end, we studied a validated *in vitro* co-culture model of sensory neurons and Schwann cells adapted to 96-well culture plates. This model allows measurement of the appearance of myelin proteins as an index of the physiological process of *in vivo* myelination. Total myelin length was quantified with an automatic image analyzer following PMP22 immunostaining. We first determined the full dose-response curves of single drugs, emphasizing their promyelinating activities. We then tested binary combinations of very low and inactive doses of each drug and compared these to the activity of the combination of the three, namely PXT3003. Whereas combination of any two drugs was not significantly active at the doses tested, combination of all three produced a synergistic improvement in myelination. These findings clearly demonstrate the necessity of using PXT3003 over its single components and highlight the value of pleiotropic combinational repurposing of drugs at low doses as a novel approach for rapid drug development in CMT1A and other disorders.

AN UP-TO-DATE REVIEW ON SWEATING DISTURBANCES IN GUILLAIN-BARRÉ SYNDROME.

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Autonomic dysfunction is frequently observed in Guillain-Barré Syndrome (GBS) and affects approximately 75% of the patients. It has been shown that the sweating function can be impaired in GBS. The aim of the present investigation is to summarize the current knowledge on sweating disturbances in GBS patients. We have used appropriate terms to systematically search for references published until 2016 and indexed in the following databases: Medline, Embase, Lilacs and Cochrane. The inclusion criteria were a diagnosis of GBS and a description of the methods used to test the sudomotor function. The search was limited to the English language. Relevant information about study design, methods of assessing the deficit of sweating, patient’s characteristics and main results were collected. We selected 13 original references for the final analyses. The majority of the studies were cross-sectional in nature and there were two longitudinal studies. The severity of sweating impairment varied according to the applied method, ranging from normal to almost sympathetic nervous system failure. In seven research papers, the sympathetic skin response was used to evaluate the sudomotor function in 99 patients, and approximately 30% demonstrated abnormal results. However, researchers used different stimulation protocols and parameters to interpret their results. Regarding whole-body sweating test, four research papers applied the thermoregulatory sweating test in 14 patients and they showed areas of anhidrosis on the lower limbs in all of them. Eight patients presented sweating impairment on the upper limbs and abdominal wall. Results on the sudomotor axon reflex test suggested a length-dependent pattern of

sweating loss according to one case report. In another study, eight GBS patients were tested only on the distal leg and foot dorsum and the authors proposed an association between post-ganglionic sudomotor function and antiganglioside antibodies. The present literature review showed that the studies of sweating disturbances in GBS patients included only small cohorts. Future studies with larger patients sample sizes are necessary to investigate the patterns of sweating loss in GBS and their changes along the follow up. Funding: grants #2013/03150-3 and #2012/07165-2, São Paulo Research Foundation (FAPESP).

SWEATING DISTURBANCES IN SENSORY NEURONOPATHY

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Sensory Neuronopathy (SN) represents a rare subgroup of peripheral neuropathies characterized by degeneration of primary sensory neurons at the dorsal root ganglia on the spinal cord. Depending on the neuronal population affected, its clinical presentation may manifest as gait ataxia, proprioceptive sensory loss and positive and negative sensory symptoms. Although a few reports have mentioned areas of anhidrosis in SN, we were not been able to find previous case series studies on the sweating function in sensory neuronopathies. The aim of the present investigation was to study the whole-body distribution of sweating on both anterior and posterior surfaces in patients diagnosed with SN. Quantitative Sensory Testing for cold and warm sensation threshold (method of *Levels*) was performed on the dorsum of the hands and feet in a randomized order. We tested the thermoregulatory sweating using a sweat chamber (44^0 to 47°C air temperature and 30% relative humidity). The oral and skin temperature was monitored and the test time did not exceed 45 min. In order to study the sudomotor axon reflex we employed the Q-SWEAT device on standardized body sites. The test was performed on both sides, simultaneously. We included seven patients (three male; mean age 50.25 years) with a mean disease duration of 67.7 months (range 24-180) and a confirmed diagnose of SN. Patients presented an asymmetrical loss of cold and warm threshold on hands or feet compared with healthy control ($P<0,05$). Regarding the TST results, we found a striking variation of sweating disturbances, ranging from small areas of anhidrosis on the trunk to complete failure of the sympathetic nervous system. Two patients underwent the axon reflex test and there was an asymmetrical and mostly distal pattern of sweating loss in one of them and a distal-symmetrical on the second one. Our findings indicate a great variability of sweating losses in SN, not overlapped to the sensory loss areas. Currently, we are testing more patients in order to confirm our results. Funding: grants #2013/26410-0, #2013/03150-3 and #2012/07165-2, São Paulo Research Foundation (FAPESP).

RATS BRED FOR LOW AND HIGH RUNNING CAPACITY MAY OFFER A NEW MODEL OF INFLAMMATORY PAIN

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Diet, exercise, and inflammation are established modulators of peripheral nervous system function, including pain. Prior work examining exercise consistently demonstrates a benefit on heightened pain from a number of acute and chronic pain models. In the present work, we investigated several parameters of peripheral nerve function relevant to pain in rats bred for high (high capacity runners, HCR) or low running capacity (low capacity runners, LCR). The longtime selective breeding of these rat substrains has created divergent intrinsic aerobic capacities and predisposition of metabolic conditions between LCR and HCR rats. Examination of the role of sex in the development of chronic pain has established key differences in males and females. To understand gender specific differences, this study focused on female rats to understand the role of metabolic status and peripheral nerve function in females. Our analysis identified numerous parameters of peripheral nerve function relevant to pain and neuropathy that are different among LCR and HCR female rats. LCR female rats display reduced hind paw mechanical sensitivity, increased hind paw intraepidermal nerve fiber density and TrkA-positive epidermal axons, increased numbers of Langerhans and mast cells in the hind paw dermis, and increased overall fat mass relative to body weight compared to female HCR rats. Examination of sensory and motor nerve conduction velocities, thermal sensitivity, and mRNA expression of selected genes relevant to peripheral sensation found no differences between HCR and LCR females. Together these results suggest that a genetic component of aerobic capacity and metabolic status can influence sensory sensitivity and specific aspects of inflammation and immune responses in peripheral tissues, which may lead modify the animal's responses to tissue damage and painful stimuli. The LCR and HCR rat model will provide a useful model in the future to assess the involvement of metabolic status in the development of pain.

EFFICACY AND SAFETY OF THREE DIFFERENT DOSAGES OF IVIG (PANZYGA®) IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLY(RADICULO)NEUROPATHY (ProCID STUDY) – DESIGN OF A PHASE 3 STUDY

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IVIG is often considered treatment of first choice in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) because of its rapid onset of action and its relatively safe long-term adverse event profile. Clinical trials published so far focused on a loading dose of 2.0 g/kg IVIG and/or a standard maintenance dosage of 1.0 g/kg IVIG once every 3 weeks, but have not investigated different dosing options. This study is a prospective, double-blind, randomized, parallel group, multi-center phase III efficacy study and will be conducted in 44 centres in Canada, EU, Russia, Ukraine and Australia. 140 adult patients with definite or probable CIDP according to the EFNS/PNS Criteria will be enrolled and randomized 1:2:1 to receive either 0.5 g/kg or 1.0 g/kg or 2.0 g/kg IVIG (panzyga®) for seven maintenance infusions at 3-week intervals during the Dose-evaluation Phase. The starting loading dose will be 2.0 g/kg IVIG (panzyga®) for all patients. Primary objective: Efficacy measured as percentage of responders (decrease in adjusted INCAT score by at least 1 point) in the 1.0 g/kg IVIG (panzyga®) arm (given every 3 weeks) at Week 24 as this should corroborate the existing and published evidence on efficacy of IVIG in CIDP. Secondary outcome: percentage of responders at week 24 in the 0.5g/kg and 2.0 g/kg IVIG (panzyga®) arms relative to baseline and compared to the 1.0 g/kg arm. The ProCID study aims to confirm published clinical results obtained with the 1.0 g/kg standard dose and will in addition evaluate one higher and one lower maintenance dose, with the aim to offer CIDP patients a more adequately dosed and effective treatment policy.
* Este medicamento no se encuentra comercializado en España.

RATE OF PROGRESSION IN PEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

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Understanding the rate of disease progression in patients with Charcot-Marie-Tooth disease (CMT), both within and between subtypes is important for clinical prognosis and is crucial for clinical trial design. Due to the progressive nature of CMT, intervening at the earliest stages of the disease is a priority. Measuring progression of a disease with both motor and sensory deficits requires a multi-item composite scale. The CMT Pediatric Scale (CMTPedS) is a well-tolerated psychometrically robust 11-item scale measuring fine and gross motor function, strength, sensation and balance for children and adolescents aged 3-20 years with CMT. The aim of this study was to determine the rate of disease progression of children and adolescents within and between genetic subtypes of CMT. 206 (103 female) participants aged 3-20 years enrolled in the Inherited Neuropathies Consortium were included in this study. Demographic, anthropometric and diagnostic information were collected at baseline and 2-year follow-up. Disease progression was measured with the CMTPedS. On average CMTPedS scores progressed at a rate of 2.4 points over 2-years (14% change from baseline, $p<0.001$). There was no difference in rate of disease progression between males and females. Of the most common genetic subtypes, 111 participants with CMT1A/PMP22 duplication progressed by 1.8 points (12% change from baseline, $p<0.001$), nine participants with CMT1B/MPZ mutation progressed by 2.2 points (11% change), six participants with CMT2A/MFN2 mutation progressed by 6.2 points (23% change) and seven participants with CMT4C/SH3TC2 mutation progressed by 3.0 points (12% change). Participants with CMT2A progressed faster than those with CMT1A ($p=0.02$). Children with CMT1A progressed consistently during childhood and adolescence while children with CMT1B and CMT2A progressed faster during childhood than adolescence. Overall, children with CMT progress at a significant rate over 2-years according to the CMTPedS. Understanding the rate at which affected children deteriorate is essential for adequately powering clinical trials of disease-modifying interventions.

TARGETED NEXT-GENERATION SEQUENCING (NGS) PANELS IN CMT: A RETROSPECTIVE COMPARATIVE STUDY IN UK AND US TERTIARY REFERRAL CENTRES

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In recent years, targeted NGS panels have changed the diagnostic work-up in patients with inherited neuropathies. However, there is limited data on the impact of targeted NGS panels on the diagnosis of CMT patients in everyday practice. The aim of this study was to investigate the impact of targeted NGS panels on the diagnosis of CMT across two tertiary referral centres in the United Kingdom (London) and United States (Iowa). In London, 128 patients with a diagnosis of CMT (previous PMP22 duplication and common CMT genes excluded in appropriate cases) underwent targeted NGS panel sequencing covering 50 genes associated with CMT and 26 additional genes associated with HSP or ALS. A variable number of genes, ranging from 11 to 76, were analysed depending on the clinical phenotype of the patients. A definite molecular diagnosis was achieved in 37 cases (28%) including pathogenic and likely pathogenic mutations in SH3TC2 (5 cases), GJB1 (4 cases, including 2 cases with mutations in the promoter and 3'UTR regions), GDAP1 (3 cases), FGD4 (3 cases), AARS (2 cases), IGHMBP2 (2 cases), MPZ (2 cases), NEFL (2 cases). VUS were further identified in 20 patients. The diagnostic rate was higher in demyelinating CMT cases (21/42, 50%), compared to cases with axonal CMT (10/53 19%), dHMN (4/20, 20%) and HSN (1/13, 8%). In Iowa, 50 patients were investigated by NGS panels covering 18 to 79 genes associated with CMT. A molecular diagnosis was reached in 22/50 (44%), and in particular 8/10 (80%) demyelinating and 14/40 (35%) axonal CMT cases. The most frequent genes identified were GJB1 (6 cases), MFN2 (4 cases), SH3TC2 (3 cases) and IGHMBP2 (2 cases). VUS were identified in 22 patients, including 5 cases with novel variants in AARS, warranting additional testing such as segregation of the variant in the family or functional validation studies. In clinical practise, targeted NGS panels represent an effective approach for the diagnosis of CMT. The lower diagnostic rate in London is likely to be due to prior Sanger sequencing and exclusion of mutations in common CMT genes in this patient population.

DIAGNOSTIC YIELD OF A 6,000 DISEASE-ASSOCIATED GENE FOCUSED EXOME IN CMT AND COMPLEX NEUROPATHY CASES: AN EXPLORATORY STUDY

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More than 80 genes are known to cause CMT and an even larger number are known to cause peripheral neuropathy as part of a more complex neurological disorder. Despite the use of custom panels, a significant proportion of patients with inherited neuropathy have no molecular diagnosis. The aim of this study was to investigate the diagnostic yield of a 6000 disease-associated gene exome (SureSelect Focused Exome, Agilent Technologies, Santa Clara CA, USA) in the diagnosis of CMT and in cases with complex neurological syndromes associated with neuropathy. Thirty-one patients with molecularly undiagnosed inherited neuropathy were analysed with SureSelect Focused Exome sequencing. Six patients had a more complex phenotype including learning difficulties, cerebral white matter changes, ataxia and pyramidal tract involvement. A genetic diagnosis was achieved in 13/30 (43%) of cases by detecting a mutation in CMT-associated genes MPZ (2 cases), AARS, NEFL, BSCL2, BICD2 and TRPV4. Of note, six cases had mutations in genes which are not covered by currently available diagnostic targeted NGS panels, including KIF1A, POLG, MME (2 cases), DNAJB2, and a novel candidate gene. The average coverage was higher compared to the usual coverage of whole-exome sequencing; 95% of the targets were covered at 30x or more, and 98% of the targets were covered at 10x or more. This study provides evidence that the SureSelect Focused Exome is a useful tool for the diagnosis of CMT and complex neurological disorders and provides further insight into the phenotypic spectrum of genes associated with inherited neuropathy.

FUNCTIONAL VALIDATION OF NON-CODING VARIANTS OF GJB1 IN PATIENTS WITH CMTX1

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Changes in the cis-regulatory sequences of a gene's untranslated regions (UTR) are increasingly recognised as a significant cause of inherited disease in humans. For example, variants in the non-coding region of GJB1 account for 10% of all mutations in our cohort of CMTX patients. One of the biggest challenges in analysing the large number of non-coding variants in a gene is identifying those that are disease-causing and those which are polymorphisms. The aim of this study was to implement a reliable method for the in-vitro functional validation of non-coding variants in the promoter and 3'UTR regions of GJB1. In our cohort of CMTX patients we have previously identified seven mutations (c.-592_591insT, c.-570G>A, c.-529T>G, c.-529T>C, c.528T>C, c.-527G>C, c.-459C>T) in the promoter region and one novel mutation in the 3'UTR (c.876C>T), which were considered likely to be pathogenic based on the clinical phenotype, segregation in affected family members and absence in control databases. We have now generated a luciferase-based reporter system and optimised it in a Hela cell line. Mutations in the promoter region were generated by site-directed mutagenesis using a commercially available GJB1 promoter clone (Genecopoeia). Our preliminary results show a reduction of luciferase activity for the c.-528T>C and c.-592_591insT mutations compared to the wild-type promoter. This difference was increased when transcription factors SOX10 or EGR2 were co-transfected with the 528T>C and c.-592_591insT mutations respectively. Validation of other variants is currently ongoing. If successful, our study will provide a useful tool for the validation of mutations in non-coding regions of GJB1. Moreover, it will constitute a proof-of-principle approach to the functional validation of non-coding variants in other CMT genes known to cause disease by a loss of function.

CHARCOT MARIE TOOTH DISEASE TYPE 2 (CMT2P) DUE TO LRSAM1 MUTATIONS: CLINICAL AND GENETIC FINDINGS

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Recessive and dominant mutations in leucin-rich repeat and sterile alpha-motif-containing 1 (LRSAM1) have been associated with CMT2P. LRSAM1 is a ubiquitin E3 ligase containing a RING domain in its C-terminal, which is crucial for correct protein folding and ubiquitination activity. To date, the majority of dominant mutations reported have resulted in a frame shift disrupting a major portion of the RING-domain, although point mutations in this domain have also been described. The aim of this study was to report the prevalence, clinical features and genetic findings of patients with CMT2P in our centre. We performed targeted next-generation sequencing in 57 genetically undiagnosed CMT2 patients and identified 6 cases with heterozygous mutations in LRSAM1 (10.5%) from 6 unrelated families. The mutations Identified included frameshift insertions and deletions, a non-frameshift deletion and non-sense and missense point mutations. All of the mutations were novel and were located in or flanking the RING domain. The average age of disease onset was in the 3rd decade but an earlier onset was reported in two cases. Four had a positive family history in keeping with autosomal dominant inheritance. Symptoms at presentation were heterogeneous and encompassed distal numbness, unsteadiness, distal weakness of upper or lower limbs and foot deformities. Positive sensory symptoms, including tingling and shooting pains, and cramps were also frequently reported. Neurological examination showed mild to moderate distal atrophy and weakness, with early ankle plantar flexion involvement in three patients. Loss of vibration and reduced joint position sense were often prominent in the lower limbs and appeared to be disproportionate to the degree of weakness and impairment of pinprick sensation. Ankle jerks were absent but knee and upper limb reflexes could be normal or brisk. After an average disease duration of 20 years, all but one patient was able to walk independently. Nerve conduction studies showed a sensory and motor axonal neuropathy with normal conduction velocities. Our study highlights that mutations in LRSAM1 are a relevant cause of CMT2 and are associated with prominent large fibre sensory loss.

DIAGNOSTIC CHALLENGES IN THE MOLECULAR DIAGNOSIS OF CMT IN THE ERA OF NEXT GENERATION SEQUENCING (NGS)

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In recent years, the implementation of NGS panels for the molecular diagnosis of CMT has increased the number of patients with a genetic diagnosis. Nevertheless the interpretation of a particular variant as disease causing can be challenging especially when multiple variants are identified in a single patient. We report two illustrative cases of such challenges. The first index case was born of non-consanguineous healthy parents. He presented with

falls in early childhood. Over the years he developed foot deformities and progressive length dependent weakness. He had multiple orthopaedic operations to his feet. The past history was also notable for kyphoscoliosis, sensorineural deafness from the age of 30 and bilateral cataracts. Nerve conduction studies at the age of 54 revealed a demyelinating neuropathy consistent with the clinical phenotype of CMT1. His younger brother had a similar, although more severe phenotype. A LITAF (c.115C>T,p.Pro39Ser) mutation was identified by Sanger sequencing and was present in both affected brothers but also in the unaffected sister. NGS for CMT1-associated genes was therefore performed and identified two compound heterozygous pathogenic mutations detected in SH3TC2 (c.2860C>T, p.Arg954*;3303delG, p.Arg1101Serfs*15), which segregated with the disease in the family.
The second case describes a brother and sister with early onset demyelinating CMT associated with scoliosis and cranial nerve involvement. The male proband underwent NGS and a single previously reported pathogenic intronic splice-site mutation in SH3TC2 (c.286-2A>C) was found. Relative read-depth analysis of NGS was performed to look for possible copy number variants in SH3TC2, thus identifying a deletion of exon 7, which was confirmed by long PCR.

COWCHOCK SYNDROME, 2 FAMILIAL CASES WITH A NEW MUTATION IN *AIFM1* GENE

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Charcot-Marie-Tooth disease (CMTD) defines a clinical and genetically heterogeneous group of inherited peripheral neuropathies characterized by chronic motor and sensory impairment. The type CMTD-4 also known as Cowchock syndrome, is the product of the mutation in the apoptosis inducing factor mitochondria associated 1 gene (*AIFM1*). It is a slowly progressive, recessive, X-linked disease characterized by axonal neuropathy, deafness, and cognitive impairment.
Our purpose is to describe 2 new cases, brothers, children of non-consanguineous parents, with a characteristic phenotype and a new mutation in the *AIFM1* gene.
Both siblings present from childhood, progressive weakness in lower limbs with diffuse amyotrophies. Needing tenotomy before the 7 year due to equinovarus foot. Likewise they develops sensory deafness and one of them requires unilateral support at 39 and the other wheelchair at 38, this one need a pacemaker for an atrioventricular block at 40.
With brain functions and normal language, sensorial deafness, proximal and distal weakness in the four limbs with intense amyotrophies, predominantly distal. Tactile and painful sensitivity decreased in glove and sock pattern.
An extensive metabolic and biochemical study was normal. The electroneurography demonstrates an axonal neuropathy without response in most of the nerves explored. The electromyography shown a myogenic pattern with distal predominance. Brain MRI was normal in both cases. Through a genetic study by exoma targeting 53 genes associated with CMT and inherited related neuropathies was identified the homicigosis mutation in the *AIFM1* gene (p.Glu366Lys), located in the chromosomal region Xq26.1 (CMTX4).
Cowchock syndrome is a rare entity, with few cases described in the literature. The in silico analysis indicates in 7 of the 9 predictors used (*PROVEAN, SIFT, PolyPhen2, LRT, MutationTaster, MutationAssessor* and *CONDEL*), that it is a deleterious variant.

TREATMENT OF PARAPROTEINAEMIC NEUROPATHIES – A SINGLE-CENTRE AUDIT

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We audited all patients with peripheral neuropathy caused by a paraprotein, who received treatment and attended King's College Hospital peripheral nerve service between 2004-16. Patients were identified retrospectively from our database of patients attending the peripheral nerve outpatient clinic. Clinical information was obtained retrospectively from hospital electronic patient records. We excluded patients with POEMS syndrome or in whom the neuropathy was not felt to be caused by the paraprotein. We identified 61 patients with a diagnosis of paraproteinaemic neuropathy. We excluded four who did not fulfill the diagnostic criteria and eleven who had received no treatment or were under diagnostic study. We included 46 patients in the final audit. 45 (98%) had IgM paraprotein. The haematological diagnosis was monoclonal gammopathy of undetermined significance (MGUS) in 65%, Waldenstrom´s macroglobulinaemia 30%, and lymphoma or plasmacytoma 5%. After treatment, overall 13 (28%) patients improved neurologically, 11 (24%) stabilised, and 22 (48%) worsened. In the 19 patients who received more than one type of treatment, we analysed outcomes according to the most powerful treatment received. 23 patients received rituximab alone of which 5 (22%) improved, 6 (26%) stabilised and 12 (52%) worsened. Nine patients received rituximab combined with cyclophosphamide or bendamustine, of which 3 (33%) improved, 2 (22%) stabilized and 4 (44%) worsened. Eight patients received intravenous immunoglobulin, of which 3 (38%) improved, 2 (25%) stabilized and 3 (38%) worsened. Four patients received other chemotherapy, of which 2 improved, 1 stabilised, 1 worsened. Two patients received corticosteroids and both worsened. There was

improvement in 7/29 (24%) with MAG antibodies and 6/17 (35%) without. There was improvement in 5/26 (19%) with MGUS and 5/14 (36%) with haematological malignancy. There was improvement in 11/32 (34%) with kappa light chains and 2/14 (14%) with lambda. Factors associated with better outcome (by univariate analysis) were negative MAG antibodies, kappa light chain, and haematological malignancy. There was no significant difference between treatments in the proportions who improved.

SWITCHING FROM IVIG TO FLEXIBLY-DOSED SCIG IN PATIENTS WITH CIDP AND MMN: CLINICAL AND PATIENT EXPERIENCE

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Treatment of patients with autoimmune neuropathies such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) has centred on the use of intravenous immunoglobulin (IVIg). However, IVIg therapy is associated with systemic side-effects, treatment wear-off effects and regular hospital attendance. Subcutaneous immunoglobulin (SCIg) is an efficacious alternative that can be flexibly dosed, self-administered at home and avoids the 'peaks' and 'troughs' observed with IVIg. These factors may combine to improve patient satisfaction and alleviate hospital capacity issues. Here, we report on clinical and patient experience of switching from hospital-based IVIg to home-based manual push SCIg for the treatment of CIDP and MMN. This was a clinical case series of 10 patients (8 CIDP, 2 MMN; mean age 59.5 years) who were clinically stable on IVIg and wished to switch to manual push SCIg. Starting SCIg dose was equivalent to the final IVIg dose for each patient (mean 0.23 g/kg week). Clinical efficacy (Medical Research Council sum score, 10-m walk, modified Inflammatory Neuropathy Cause and Treatment score, Overall Neuropathy Limitations Scale, Romberg test) and patient-reported outcomes (36-item Short Form Health Survey [SF-36], Life Quality Index [LQI]) were assessed at baseline and at regular intervals until the final visit (10–14 months after switching). At baseline, patients cited 'convenience' as their primary reason for switching to SCIg. Eight patients completed the full assessment period and successfully undertook administrations at home (via hospital-at-home service in 2 cases). Dose adjustments, based on clinical need, were required in 6 patients. Treatment efficacy and patient quality of life, measured by SF-36, were maintained after switching to SCIg; overall patient satisfaction, measured by LQI, increased from 75% to 90%. In the LQI, 'convenience', 'travel time/cost' and 'interference-work' were significantly improved ($p<0.05$) after switching to SCIg therapy. Adverse events included mild erythema and localised swelling, as expected for a 20 mL subcutaneous injection. These findings suggest that manual push SCIg therapy is a viable alternative to IVIg for patients with CIDP and MMN, as it maintains disease stability, is more convenient for patients and may help ease hospital capacity concerns.

A RETROSPECTIVE AUDIT OF IVIG INFUSION RATES IN THE TREATMENT OF AUTOIMMUNE NEUROLOGICAL DISEASE

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Intravenous immunoglobulin (IVIg) is used to treat a number of chronic autoimmune neurological diseases. In most centres, infusions are given at slow rates as there is a perception that this reduces the risk of adverse events (AEs). This results in longer in-patient admissions, or frequent day case attendances, impacting on both the patients' quality of life and hospital capacity. However, there is little evidence to suggest that slow infusion rates are required. We used the manufacturer recommendations to optimise infusion rates and reduce the time patients spend in hospital. We report a retrospective audit which describes the impact of different IVIg infusion rates on patients' clinical condition. The audit comprised three 6-month assessment periods: January–June 2015 (cohort 1; infusion rates of 1.2 ± 0.1 mL/kg/hr, n = 27); January–June 2016 (cohort 2; 2.4 ± 0.1 mL/kg/hr, n = 42) and July–December 2016 (cohort 3; 3.9 ± 0.2 mL/kg/hr, n = 39). Clinical data were reviewed to determine: patient demographics, duration of infusion; time spent in hospital; and incidence of AEs. The three cohorts were well matched in terms of patient demographics (14 patients were treated in all 3 treatment periods). Cohorts 2 and 3 had significantly shorter treatment episodes than cohort 1 (3.2 and 2.7 vs. 4.1 hours, $p<0.01$), spent less time on the unit over the 6 month period (25.6 and 20.3 vs. 39.4 hours, $p<0.05$) and had fewer admissions/patient (6.5 and 5.9 vs. 8.5, $p<0.05$). The overall incidence of confirmed AEs (mainly headaches) was similar across the cohorts (cohort 1: 15%; cohort 2: 19%; cohort 3: 18%). These findings indicate that increases in IVIg infusion rate are well tolerated and significantly reduce treatment time, which benefits patients and offers potential cost savings and reduced pressures on hospital capacity for healthcare providers.

DEVELOPMENT OF A SUBACUTE ANTI-GANGLIOSIDE ANTIBODY-MEDIATED MOUSE MODEL OF GBS

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One mechanism of injury in the acute motor axonal neuropathy (AMAN) form of Guillain-Barré syndrome (GBS) is the attack of peripheral nerve axons by anti-ganglioside antibodies (AgAbs). Rodent models have demonstrated that that binding of these antibodies activates the complement cascade, resulting in the insertion of the terminal component, membrane attack complex (MAC) into the axonal membrane. Complement activation also results in the release of anaphylatoxins, which are known to recruit phagocytic immune cells to the site of injury. Our

current in vivo mouse model of AgAb and complement-mediated injury are acute and severe, resulting in respiratory distress over several hours of such magnitude to warrant termination of experimental procedures. To observe and potentially target immune cell infiltration following AgAb and complement-mediated injury, a subacute model extending over days is required. Here, we demonstrate the development of such a model. To compare differences in immune cell infiltration subacutely under control and injury conditions, mice with endogenous expression of eGFP in monocytes and macrophages underwent a modified AgAb and complement-mediated injury, resulting in a less severe phenotype than previously published models. Six days following injury, immune cells in the diaphragm were compared by immunofluorescence and flow cytometry. Flow cytometry found overall presence of neutrophils was significantly increased in the diaphragm. Macrophages were also increased in injured mice, although did not achieve statistical significance at this timepoint. These results were reflected in immunofluorescent staining of the diaphragm where eGFP+ macrophages were quantified surrounding the neuromuscular junction (the primary injury target in this model). The development of an extended mouse model of AgAb and complement-mediated injury is important, since acute models do not take into consideration either the late-term effects of complement-mediated activation at the nerve membrane, or the recovery phase. Future studies will look at the effect of inhibiting complement activation on the presence of immune cells in distal motor nerves.

UNRAVELLING THE DISEASE MECHANISMS UNDERLYING THE DHMN1 INSERTION

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Family-54 is a large Australian family with an autosomal dominant form of dHMN (DHMN1: OMIM %182960) - a group of length-dependent neurodegenerative disorders affecting the lower motor neurons leading to chronic disability. We recently reported a novel 1.35 Mb chromosomal insertion within the DHMN1 locus which we hypothesise is likely to cause disease by dysregulating the expression of one or more nearby genes. Studying gene dysregulation in peripheral nerve disease is challenging as the relevant tissues (spinal cord and peripheral nerve) are not easily accessible in patients. Therefore, alternative strategies are needed to elucidate the disease mechanisms and pathways involved in peripheral nerve degeneration. To address this problem, we have devised a two-tiered strategy to assess dysregulation of candidate genes using patient lymphoblast and fibroblast cell lines. These cell lines can be easily established, are minimally invasive to obtain, and will harbour the natural mutation and genetic background of patients. Our strategy firstly uses lymphoblast gene expression profiles as an initial screening tool to prioritise candidate genes for assessing altered expression. Differentially expressed genes will then be modelled in *C.elegans* where behavioural and nerve morphology can be assessed. Using RT-PCR, we have screened 21 DHMN1 candidate genes in patient and control lymphoblast cell lines. Eighteen candidate genes were expressed in lymphoblasts. Twelve of the eighteen genes were prioritized for further analysis based on expression in both lymphoblast and neural tissues. Quantitative analysis using qRT-PCR TaqMan assays revealed that *UBE3C,* was differentially expressed between patients and controls. It is important that patterns of differential expression can be recapitulated in neural cell-specific models. As part of our second strategy, we have generated patient and control induced pluripotent stem cell derived motor neurons (iPSC-MNs) from reprogrammed fibroblasts. Using this model, we will perform RNA-seq and qPCR experiments to examine disease-relevant alterations in gene expression in neural tissue. We predict that utilization of these two strategies will shed light on the pathogenic mechanisms underlying the DHMN1 insertion and provide useful insights of pathways leading to peripheral nerve degeneration.

INHIBITION OF COMPLEMENT IN GUILLAIN-BARRÉ SYNDROME: THE ICA-GBS STUDY

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The outcome of Guillain-Barré syndrome remains unchanged since plasma exchange and intravenous immunoglobulin were introduced over 20 years ago. Pathogenesis studies on GBS have identified the terminal component of complement cascade, the membrane attack complex, as a key disease mediator and thus a therapeutic target. The Inhibition of Complement in Guillain-Barré Syndrome (ICA-

GBS) trial looked at the first use of C5 pathway inhibition with eculizumab in humans with GBS in a randomised, double-blind, placebo-controlled trial. Its primary outcome was to look at safety and tolerability of administration concomitantly with IVIg and in the context of severe (GBS disability score 3 or greater) disease. Participants were recruited for a 6 month period, with regular follow up. 28 subjects were screened, with 8 (29%) being randomised. The two main causes for failure to proceed were participant concerns around eculizumab side effect profile, specifically the meningitis risk, and also intercurrent infection precluding treatment. Five received eculizumab for four weeks, alongside standard intravenous immunoglobulin treatment, with 3 receiving placebo. The safety outcomes, monitored via adverse events capture at each trial visit, showed eculizumab to be well tolerated and safe when administered in conjunction with IVIg. The most common adverse events were mild derangement in transaminases or infection. There were no infusion reactions. Primary and secondary efficacy outcomes were captured via GBS disability scores, MRC sum scores, Rasch Overall Disability Scores and Overall Neuropathy Limitation Scores. For the primary efficacy outcome at 4 weeks after recruitment, 2 of 2 placebo and 2 of 5 eculizumab-treated subjects had improved by 1 or more grades on the GBS disability score. All patients had improvements in other measured parameters. This trial highlights the challenges in recruiting acutely unwell patients, due to time constraints and intercurrent infection. Although the small sample size precludes a statistically meaningful analysis, these pilot data indicate further studies on complement inhibition in GBS are warranted.

CHARCOT-MARIE-TOOTH 2W. A NEW MUTATION?

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Charcot-Marie-Tooth disease (CMT) affects about one in 2.500 people. Currently more than 44 genes have been identified, with the most different phenotypes. The majority of cases in Western countries are autosomal dominant and classified as demyelinating and axonal according to electroneuromyography (ENMG). The clinical condition is characterized by weakness and predominant sensory changes in the feet and hands. Sometimes there are different phenotypes. Recently, variants in heterozygotes in the HARS gene (Histidil-tRNA synthetase) have been described associated with CMT called type 2W.To report a case of CMT-sensitive phenotype with a probable new mutation in HARS gene (p.Leu41Arg).A male patient, adopted son, Caucasian, drug addict, for three years suffered pain in lower limbs, of great intensity, refractory to drug treatment. The examination showed retrognathism, abolition of patellar and achilleas reflexes, painful and thermal anaesthesia and apalesthesia in the feet.The ENMG showed reduced sensory action potentials in sural and superficial fibular nerves. Laboratory investigations for painful polyneuropathy of thick and fine fibres was normal. Sural nerve biopsy revealed axonal predominance neuropathy. Exome sequencing revealed a mutation in the HARS gene with a pathogenic variant in heterozygosity, with replacement of the amino acid leucine at position 41 by arginine. Our patient, although we did not know the antecedents, presented painful polyneuropathy, whose genetic research, although not unequivocal, indicated a variant called CMT W. Few cases of this variant were described, with several mutations. Our case revealed mutation hitherto unknown (p.Leu41Arg). We conclude by the importance of a thorough genetic evaluation, in cases of sensory polyneuropathy of unknown cause.

A RANDOMIZED CONTROLLED TRIAL OF THE EFFICACY, SAFETY, AND TOLERABILITY OF LACOSAMIDE IN PATIENTS WITH GAIN-OF-FUNCTION NAv1.7 MUTATIONS-RELATED SMALL FIBER NEUROPATHY, THE LENSS STUDY

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Small fiber neuropathy (SFN) is a condition that affects the small Aδ- and C-fibers, leading to severe neuropathic pain and autonomic dysfunction. Several sodium channel gene mutations have been found in patients with SFN, with SCN9A-gene mutations being the most frequent. Because current available sodium channel blockers are not selective for $Na_V1.7$, these treatments often result in numerous side effects. Lacosamide is an anticonvulsant that targets specific sodium channels with a slow-inactivation state, while sparing those with normal activity. Several mutations of the SCN9A-gene with an impaired slow-inactivation of $Na_v1.7$ have been found in patients with SFN. Therefore, a positive effect of lacosamide on pain reduction in these patients is expected. The primary objective of this study was to determine the effect of lacosamide versus placebo on pain in subjects with *SCN9A*-associated SFN. Secondary objectives were to determine the effect of lacosamide on autonomic symptoms, sleep interference, and quality of life, and to examine the safety and tolerability. The Lacosamide-Efficacy-'N'-Safety in SFN (LENSS) study was a randomized, placebo-controlled, double-blind, crossover-design study. Subjects were randomized to start with lacosamide and end with placebo or vice versa. During both of the two phases of the study, the subjects were treated for a period of eight weeks of 200mg BID, preceded by a titration period, and ended by a tapering period. Patients filled in a pain diary twice daily and scored a set of validated questionnaires on autonomic symptoms, sleep interference, and quality of life at multiple study visits. In total 25 patients with *SCN9A*-associated SFN were

included between November 2014 and February 2017. The subjects had a median age of 58 years, ranging from 24 to 78 years. Sixty percent of the patients were female. The final results of the study, including the primary and secondary outcomes, will be presented.

DEXAMETHASONE REDUCES THE FOREING BODY RESPONSE TO PARYLENE-C INTRANEURAL IMPLANTS IN RATS

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Intraneural interfaces must be in intimate contact with nerve fibres to have a proper function, but it has been shown that this is compromised due to the foreign body reaction (FBR). This FBR is the first response of the nonspecific immune system against an implanted device and is characterized by a first inflammatory phase followed by a second antiinflammatory and fibrotic phase. This process results in the formation of a tissue capsule around the interface causing function loss due to the physical separation between the active sites of the electrode and nerve axons. Taking this into account, here we have tested several anti-inflammatory drugs such as dexamethasone, ibuprophen and maraviroc to reduce macrophage activation as well as clodronate liposomes to reduce monocyte/macrophage infiltration. Moreover, sildenafil have been administered as an antifibrotic drug to reduce collagen deposition in a FBR model with longitudinal Parylene C-based intraneural devices implanted in rat sciatic nerve. Briefly, animals were systemically treated with dexamethasone, ibuprophen, sildenafil, maraviroc or clodronate liposomes for two weeks, and nerve damage, inflammatory reaction and matrix thickness around the implant were assessed. Treatment with dexamethasone, ibuprophen or clodronate liposomes significantly reduced the inflammatory response in the nerve in comparison to saline group while sildenafil or maraviroc had no effect on iba1 positive cells infiltration in the nerve. However, only dexamethasone was able to significantly reduce the matrix deposition around the implant after two weeks of treatment. These results support the idea that inflammation triggers the foreign body response in peripheral nerves and a potent anti-inflammatory treatment with dexamethasone could have a beneficial effect on lengthening intraneural interfaces lifespan.

TIME-COURSE CHARACTERIZATION OF FOREIGN BODY REACTION TO IMPLANTED DEVICES IN RAT PERIPHERAL NERVE

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Intraneural interfaces functionality decreases over time, among other factors, due to the foreign body response (FBR), which encapsulates the implanted devices and physically separates the active sites from the nervous tissue. Here we have studied the FBR to parylene C or polyimide thin devices implanted in rat sciatic nerves, assessing thickness of the tissue capsule, signs of inflammation and nerve damage. We have characterized the responsible cells of this response and several molecular mediators over 8 months of implant to find differences between the FBR to both materials. After 2 weeks of implant, the inflammatory response due to the surgery was already decreased, whereas in the implanted nerves it reached its highest levels to then decrease at chronic time points. Besides, the amount of foreign body giant cells (FBGC), as a result of macrophage fusion, found in the tissue capsule around the implant also increases progressively to reach a maximum after 2 weeks. On the other hand, molecular analysis of the environment revealed a peak of inflammatory cytokines during the first day of implant to return to standard levels thereafter. However, an increase on CCLs molecules was found at later time-points for both materials. With regard to the capsule thickness, all the devices were surrounded by a tissue deposition which appeared soon after the implantation. However, in the case of polyimide devices, the tissue capsule showed a peak 2 weeks after the implant and signs of remodeling thereafter, while the parylene C devices showed a second increase from 8 to 16 weeks in comparison to polyimide devices. Immunohistochemical and electron microscopy analysis revealed two different cell types implicated in the FBR in nerve to both materials: macrophages, in close contact with the interface, and fibroblasts which appear after 8 weeks surrounding the tissue capsule. Although further analyses are needed to elucidate the differences in the FBR to parylene C and polyimide polymers, these results can help to determine therapeutic targets in order to reduce this response and to improve the intraneural interfaces lifespan.

VALUE OF ANTI-HNK1 ANTIBODIES IN ANTI-MAG NEUROPATHIES: AN ANALYSE OF 144 SERA.

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Peripheral neuropathies with antibodies against Myelin Associated Glycoprotein (MAG) are chronic sensory neuropathies characterized by the presence of an IgM monoclonal gammopathy and high levels of anti-MAG antibodies. These antibodies recognize a specific epitope called Human Natural Killer 1

(HNK1) shared by NK lymphocytes and several components of the peripheral nerve (MAG, P0, PMP22, SGPG, phosphocan). Recently an ELISA test has been developed to detect antibodies against HNK1 epitope.
Our objectives were to determine the sensitivity and the specificity of anti-HNK1 antibodies in the diagnosis of anti-MAG neuropathy and to know if these antibodies were correlated with the severity of the disease.
Anti-HNK1 antibodies were assessed in 42 anti-MAG neuropathies and in 102 negative controls: 29 chronic inflammatory demyelinating polyradiculoneuropathies (CIDP), 3 Miller Fisher syndromes, 11 sensory neuronopathies, 58 length-dependant axonal sensory polyneuropathies, 5 healthy controls. In anti-MAG neuropathies, were recorded age, disease duration, INCAT sensory sum score (ISS), Overall Neuropathy Limitation Scale (ONLS), Rasch-built Overall Disability Scale (RODS), MRC sum score, anti-MAG antibodies titer, peak dosage of the IgM monoclonal gammopathy. Anti-HNK1 antibodies were measured with GanglioCombi™ MAG ELISA test and anti-MAG antibodies with Anti-MAG Autoantibodies ELISA test both from Buhlmann company.
Anti-HNK1 antibodies were positive in 41/42 anti-MAG neuropathies, and in 1/102 controls (sensitivity 98%, specificity 99%). In anti-MAG neuropathies, anti-HNK1 titer was correlated with sensory deficiency evaluated with the ISS score (r=0.5, p=0.006) and with disability evaluated with the RODS (r= -0.4, p=0.013) and ONLS scales (r=0.4, p=0.025). Anti-HNK1 titers were not related to age, disease duration, MRC sum score, anti-MAG antibodies titer, peak dosage of the paraproteinemia. Anti-MAG antibodies titers were associated with none of the characteristics of the patients with anti-MAG neuropathy.
Anti-HNK1 antibodies have good sensitivity and specificity in the diagnosis of anti-MAG neuropathy. Compared to anti-MAG antibodies, their value is that their titers are related to the disease severity. These results need to be confirmed in a larger prospective cohort.

AUTOANTIBODIES TO NODAL ISOFORMS OF NEUROFASCIN IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)is a heterogeneous and treatable immune-mediated disorder that critically lacks biomarkers to support diagnosis. Recent evidences indicate that paranodal proteins (contactin-1, contactin-associated protein-1, and neurofascin-155) are the targets of autoantibodies in a subset of patients with CIDP showing distinct clinical presentations. Particularly, these biomarkers appear to have clinical relevance and help to orientate therapeutic choice. Here, we examined five patients presenting an IgG reactivity against the nodes of Ranvier and the axon initial segment. Using a proteomic approach, cell-based assays and ELISA, we identified neurofascin-186 (Nfasc186) and neurofascin-140 (Nfasc140) as the main targets of autoantibodies at the nodes of Ranvier. Four patients displayed predominantly antibodies of the IgG4 subclass, whereas one patient presented IgG3 antibodies that activated the complement pathway in vitro. These antibodies recognized different epitopes than the previously described anti-neurofascin-155 IgG4 suggesting different pathogenic functions. Accordingly, patients with anti-Nfasc186/140 IgG showed a distinctive clinical presentation. Most patients had a severe phenotype associated with conduction block or decreased distal motor amplitude. Tremors or neuropathic pain were not observed. Four patients presented with a subacute-onset and sensory ataxia. Of interest, the neuropathy occurred concomitantly with nephrotic syndromes in two patients and with an IgG4-related retroperitoneal fibrosis in one patient. This suggested that autoantibodies could be responsible for the occurrence of both disorders. Intravenous immunoglobulin and corticosteroids were effective in three patients, and one patient improved following cyclophosphamide and rituximab treatment. Clinical remission was found to correlate with the depletion of anti-Nfasc186/140 antibodies and the loss of IgG reactivity toward the nodes of Ranvier. In addition, recovery of conduction block and of distal motor amplitude were observed following remission and suggested a nodo-paranodopathy. Our data demonstrate that nodal antigens are the target of autoantibodies in a subgroup of patients with CIDP. This emphasizes that the pathogenic mechanisms involved in chronic immune-mediated demyelinating neuropathies are broad and may include dysfunctions of the nodes of Ranvier.

NOVEL *NEFH* MUTATIONS AS A CAUSE OF AN AUTOSOMAL AXONAL FORM OF CHARCOT-MARIE-TOOTH DISEASE WITH PROXIMAL MUSCLE INVOLVEMENT

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Mutations in the neurofilament heavy (*NEFH)* gene have been recently identified as a rare cause of autosomal dominant, axonal Charcot-Marie-Tooth disease (CMT2). The clinical spectrum of this condition remains to be delineated. We report two French families with an axonal, predominantly motor, dominantly inherited form of CMT caused by two previously unreported mutations in the *NEFH* gene. Twelve patients belonging to two different families were included in the study. They displayed an axonal motor and sensory neuropathy, with no mutations in known axonal CMT2 genes. A remarkable feature in all patients was the early involvement of proximal muscles of the lower limbs, occurring approximately 10 to 15 years after the onset of motor deficit. Proximal weakness affected predominantly the iliopsoas muscle, whereas quadriceps and hamstring muscles were relatively preserved. Muscle weakness and muscle wasting progressed rapidly, with most of the patients requiring walking assistance after 20 years of disease evolution. Three patients in family 1 had brisk reflexes. Nerve-conduction velocity studies displayed evidence of a motor and sensory axonal neuropathy predominantly affecting the lower limbs. Original deletions of 2 nucleotides near the end of the coding sequence of *NEFH* were identified: in family 1, c.3008_3009del (p.Lys1003Argfs*59), and in family 2 c.3043_3044del (p.Lys1015Glyfs*47) causing a frameshift. Interestingly, this frameshift leads to the loss of the terminating codon and to the translation of 40 additional amino acids encoding a cryptic amyloidogenic element, suggesting that this type of mutations could induce protein aggregation. Consistently, we showed that overexpression of the mutated forms of NEFH in a human neuroblastoma cells induced the formation of protein aggregates. We also observed that it triggered caspase 3 activation and apoptosis. Using electroporation of chick embryo spinal cord, we confirmed *in vivo* that mutated NEFH formed aggregates and triggered apoptosis of spinal cord neurons. Altogether, this suggests that these mutations in NEFH cause protein aggregation and neurotoxicity in neurons expressing *NEFH*. Progressive loss of such neurons would explain the early motor involvement and the pyramidal signs observed in some patients. Our results provide a physiological explanation to the presence of CMT and ALS clinical features in affected patients.

FASCICULAR NERVE STIMULATION AND RECORDING USING A NOVEL DOUBLE-AISLE REGENERATIVE ELECTRODE

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Neuroprosthetic devices that are aimed to restore sensorimotor limb function of amputee patients require highly selective electrodes designed to establish a tight relationship with the nerve, allowing the bidirectional transduction of signals between nerve fibres and the interface and enabling close-loop control from the user. Differently from extra- or intraneural interfaces, regenerative nerve electrodes are designed to enable electrical interface with regrowing axonal bundles of injured nerves, aiming to achieve high selectivity for recording and stimulation. However, most of the developed designs pose an obstacle to the regrowth mechanisms due to low transparency and cause an impairment of the nerve regeneration.
In this work, we present a novel double-aisle planar regenerative electrode, a new type of highly transparent, non-obstructive regenerative electrode, which allows the selective stimulation and recording of separated nerve fascicles. The design consists of a thin and flexible double-sided electrode longitudinally inserted across a conduit thus creating two separated aisles in which regenerating fascicles can independently regrow after nerve transection.
Electrodes implanted in acutely transected nerves of rats showed the capability of selectively stimulating and recording different fascicles inserted in the aisles. Moreover, chronic implantation of the electrode in a nerve gap of 6mm after sciatic nerve section allowed for fascicle regeneration and reinnervation of distal muscles as confirmed by the high number of myelinated axons inside each aisle, good biocompatibility, and adequate nerve conduction. In addition, three and six months after implantation, independent stimulation and recording of each separately regenerated fascicle were possible.
Our results demonstrate the potential contribution of the doubled-aisle regenerative electrode to selectively interface different fascicles of an injured nerve with no deleterious effects on nerve regeneration. Therefore, this multi-aisle regenerative electrode may be suitable for neuroprosthetic applications, such as prostheses for the restoration of hand function after amputation or severe nerve injuries.

ACUTE-ONSET OF CIDP WITH IGG4 ANTI-NF155 ANTIBODIES RESISTANT TO

CONVENTIONAL THERAPIES AND RESPONSIVE TO RITUXIMAB

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Querol et al. showed that Neurofascin155 (NF155) antibodies identify a Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) phenotype characterized by severe polyradiculoneuropathy, poor response to intravenous immunoglobulins (IVIg), and disabling tremor. Neurological improvement after therapy with rituximab has been previously reported in three patients with CIDP with IgG4 anti-NF155 antibodies. Herein we describe the acute-onset of a case of CIDP positive for NF155 IgG4 antibodies resistant to conventional therapies and responsive to Rituximab. The patient is a 64 year-old woman who presented acute onset ataxia and gait disturbances; her symptoms progressed over two weeks and distal weakness, numbness and paresthesias appeared too. The nerve conduction study was suggestive for a motor-sensory polyradiculoneuropathy mainly demyelinating. The cerebrospinal fluid analysis showed elevated protein level and normal cellular count. The patient was initially diagnosed with Guillain-Barré syndrome (GBS) and treated with plasma exchange without improvement. An IVIg cycle was started with a partial relief but at the time of admission to the rehabilitation center the patient still had a marked weakness in all four limbs. After six months she presented a further clinical deterioration and she was restricted to wheelchair. There was no response to additional treatment with IVIg, while pulse corticosteroid treatment determined a significant clinical improvement.
During the next 6 months, despite the maintenance of steroid therapy, the patient presented a progressive deterioration and she was again restricted to wheelchair. Postural and intention tremor appeared at upper limbs and became progressively more disabling. Anti-NF155 Ab dosage resulted positive. Rituximab was administered at a dosage of 375 mg/m^2/weekly for 4 weeks. After three months the tremor improved, allowing her to eat independently and the patient was able to walk with bilateral support. Antibodies anti-NF155 were negative. After six months she walked without support and she was able to stitch crochet. As previously reported, in this case a CIDP positive for IgG4 NF155 developed severe polyradiculoneuropathy with predominant distal weakness, ataxia, disabling tremor and resistance to conventional therapies. Interestingly the onset was GBS-like. The correct identification of these CIDP subtypes has diagnostic, prognostic and therapeutic implications. Rituximab con be useful in these patients.

EFFECT OF NİFEDİPİNE ON SURGICALLY ANASTOMIZED PERIPHERAL NERVE REGENERATION

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It is still challenging problem to maintain motor and sensory functions of peripheral nerve after nerve transection. After the nerve injury, calcium concentration in the damaged area increases. Then the calcium ions act like cytotoxic agents in the damaged area. Nifedipine is calcium channel blocker. We aimed to investigate the effects of nifedipine on nerve regeneration by modulating calcium in the damaged area. Twenty-four Swiss albino male rats were divided into two groups. Left sciatic nerve transection surgery was performed to the all rats in both groups. Then the all transected nerves were sutured primarily with epineural interfascicular method. In the experimental group, the anastomosis sites were wrapped with a piece of gel foam soaked into diluted nifedipine solution. In the control group, the anastomosis sites were wrapped with a piece of gel foam soaked into saline solution. We evaluated the effect of nifedipine by using functional, electro-physiological and histopathological studies after the surgeries. In the postoperative second week, walking test was performed and sciatic function index was calculated. In the postoperative third week electroneuronography (ENoG) was performed. There are significant differences between two groups. Nifedipine improved nerve recovery functionally ($p<0.001$) and electro-physiologically ($p<0.001$). In the postoperative fourth week, we performed histopathological examination. In the experimental group with nifedipine there were more organized axons that reached the aim. We conclude from these results that nifedipine is an effective nerve protective agent when used locally at the anastomosis site after the transection of the nerve.

HUMAN MOTOR NEURON NEUROSPHERES AS A NEW PLATFORM TO STUDY AXONAL PHENOTYPES IN PERIPHERAL NEUROPATHIES

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The lack of effective, disease-modifying therapies for CMT highlights the need for novel preclinical models suitable for drug discovery. Studies in rodent models of CMT tend to be time-consuming, and findings so far have translated poorly into clinical trials. Primary and induced pluripotent stem cell (iPSC)-derived

neuronal cultures are an established model of neurological diseases. However, due to the random distribution of neuronal bodies and neurites that happen when plating these cells, this system is not ideal to investigate axonal, length-dependent processes like peripheral neuropathies and particularly CMT. To optimize this well-established model system, we developed a robust human platform to study axonal morphology and physiology based on motor neuron neurospheres. We differentiated motor neurons from human induced pluripotent stem cells, purified them by magnetic sorting and cultured them in suspension until they formed neurospheres. Floating neurospheres can be maintained in agitation for months as a reliable source of motor neurons. After neurospheres are platted, axons rapidly grow out of them in a radial fashion, resembling dorsal root ganglia cultures. This configuration allows for a better visualization of axons in imaging studies and for continued axonal growth over at least a 50-day period. Axons grew at an average rate of 500 micrometers/day and reached up to 1 cm in length. Neurospheres can be fixed and stained allowing for morphological analysis and investigation of protein distribution in axons. This system is also ideal for time-lapse imaging to study axonal transport of organelles and neurofilament kinetics. Lastly, our motor neuron neurosphere system lends itself well for high content screening platform. Neurospheres can be plated in 96-well plates where multiple compounds can be tested and the axons easily imaged by a high content screening microscope. In summary, we developed a new platform to investigate motor axons *in vitro,* which are particularly useful to study length-dependent processes such as inherited peripheral neuropathies and may facilitate the identification of new therapeutic compounds using high content screening systems.

ALTERED NEUROFILAMENT DISTRIBUTION IN HUMAN CMT2E MOTOR NEURON AXONS

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Mutations in the neurofilament light chain (*NFL*) gene cause autosomal dominant axonal Charcot-Marie-Tooth neuropathy (CMT2E). NFL is a major component of the neuronal cytoskeleton, and is believed to function in conjunction with NFM and NFH to provide structural support for the axon and regulate axon diameter. Despite the significant advances in understanding its biological basis, there is still no effective, disease-modifying therapy for CMT2E, in part due to the paucity of preclinical models suitable for drug discovery. The development of novel preclinical platforms that can faithfully mimic mechanisms of axonal degeneration *in vitro* would be an essential and valuable resource to better understand the biology of CMT2E and identify potential targets for therapy development. To address this, we generated control and CMT2E patient-derived motor neurons and cultured them in suspension until they formed neurospheres. Immunostaining of CMT2E neurospheres with NFL and TUBB3 antibodies revealed numerous areas of NFL accumulation in N98S CMT2E axons, resembling the accumulations of mutant NFL protein seen in the processes of catecholaminergic neuronal cell line CAD overexpressing several NFL mutants. Further analysis demonstrated that areas of NFL accumulation were also immunopositive for NFH, pNFH and NFM and that at least NFL and NFM co-localized in the same areas of deposits. Taken together, these results demonstrate that abnormal axonal neurofilament distribution is a feature of CMT2E iPSC-derived motor neurons and involve all three neurofilament subunits. We also developed an image analysis routine to allow for automatized quantification of neurofilament distribution. Preliminary quantification of NFL signal intensity revealed that axons from patients have a weaker NFL signal compared to control axons, but present several signal peaks above the range observed in controls, which related to the areas of NFL accumulation. These results suggest that NFL accumulates in certain regions of CMT2E axons but is reduced in the areas with no accumulation. These findings can be readily adapted into a high content screening platform and will be used to identify compounds able to reverse this axonal phenotype. In summary, we identified a strong axonal phenotype in human CMT2E motor neurons with potential as a screening platform for drug discovery.

PARANODAL ANTIBODIES IN AUSTRIAN PATIENTS WITH ACUTE ONSET INFLAMMATORY NEUROPATHY

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Nodal and paranodal proteins have been identified as antigens in peripheral inflammatory neuropathies, however the frequency and clinical relevance of antibody responses against these targets remain poorly investigated in GBS. Patients with acute onset inflammatory neuropathies were identified by exploration of the local databases of the Departments of Neurology and the Institute of Neurology of the Medical Universities in Innsbruck and Vienna. Patient data, electrophysiological classification and presence of anti-gangliosid antibodies were retrospectively retrieved by review of patient records. Only patients with typical clinical presentation and electrophysiological results consistent with one of the subtypes of GBS were included in the study.

Among forty-nine patients, thirty-five were classified as AIDP, six AMAN, three AMSAN, three MFS, and two pharyngo-cervico-brachial GBS. 21 of the included patients had anti-ganglioside-antibodies. Ten patients with the initial suspicion of AIDP had a disease duration of more than 6 months and were reclassified as CIDP.
All patient and twenty sera of control patients with non inflammatory polyneuropathy were screened by an optimized tissue based assay using rat brains for immune responses against surface antigens, and by cell-based assays with transfected HEK cells for antibodies against contactin1 (CNTN1), contactin2 (CNTN2), contactin-associated-protein1 (CASPR1) and neurofascin-155 (NF155).
In the tissue based assay some of the patients showed a light neuropil staining. None of GBS patient's sera had antibody reaction to CNTN1, CNTN2, CASPR1 or NF155 in cell-based assays. Among the CIDP patients, two patients demonstrated reactivity against CNTN1 with similar clinical presentation as previously described. None of the control patients had any antibody reaction to the performed tests. Our results suggest that antibody responses to CNTN1, CNTN2, CASPR1 or NF155 are absent in Austrian GBS patients, although more patients will be screened to substantiate these preliminary results. Furthermore, it remains to be established whether antibodies against CNTN1 may predict a chronic course in acute onset inflammatory neuropathies.

FREQUENCY, PROGRESSION AND THERAPY OF ATYPICAL CIDP: DATA FROM THE ITALIAN DATABASE ON CIDP

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A few variants of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been described with a frequency of 1-50%. Their relation and possible evolution into typical-CIDP remain unclear, as is their treatment response possibly because of differences in diagnostic criteria. We used the data from a web-based database on Italian patients with CIDP to determine the frequency and characteristic of these variants, the possible evolution into typical-CIDP, and their treatment response. All the patients were assessed at study entry and the disease course before inclusion was analyzed. By February-2017, we included 360 patients (227 men, 133 women), aged 12-89 years (median 59 years) with a mean disease duration of 8.2 years (range 0.5-52 years) and complete data available from 320. Based on the clinical data and our revised diagnostic criteria, 84 patients (26%) were classified to have atypical CIDP at onset and for the following two years including 29 with DADS (9%), 22 with motor CIDP (7%), 20 with sensory CIDP and 2 CISP (6.2%), 11 with Lewis-Sumner syndrome (3.5%), and 2 with recurrent cranial neuropathy. At study entry, 36 patients (43%) had progressed into typical CIDP after 2-38 years (median 5 years) while 48 (57%, 15% of total) still had atypical CIDP after 0.5-28 years (median 4 years) with a similar proportion of progression (50-60%) within each group. The diagnosis of atypical CIDP at entry fulfilled EFNS/PNS criteria in 59 (70%). CSF studies were diagnostic in 47/58 (81%) patients, nerve biopsy in 5/13 (38%), and nerve imaging in 8/9 (89%) tested patients. Similarly to typical CIDP, 81% of treated patients with atypical CIDP improved after treatment with a proportion of response varying from 67% to 100% in the different forms. Most patients with sensory or motor CIDP had however an unsatisfactory response to steroids. This study shows that he proportion of patients with atypical CIDP varies during the course of the disease with almost 50% of the patients evolving into typical CIDP within 5 years from onset. In addition, response to treatment is frequent in atypical CIDP even if not all the forms respond to the same therapies.

LIFESTYLE AND DIETARY HABITS AS PREDISPOSING FACTORS FOR THE ONSET AND PROGRESSION OF CIDP: A CASE-CONTROL STUDY FROM THE ITALIAN CIDP DATABASE

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Only few studies investigated the frequency of antecedent events and comorbidities in patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and little is known on the role of possible predisposing factors, dietary, and lifestyle habits, on the onset and progression of the disease. We used the data from a web-based database on Italian patients with CIDP to determine the frequency of antecedent events and comorbidities and the possible role of predisposing factors including lifestyle and dietary habits and exposure to toxic agents, using a structured questionnaire. Partners of patients served as controls. Impairment was evaluated using the MRC sumscore and disability with INCAT and R-ODS scales. Logistic regression was used to calculate odds ratio (OR) with 95% confidence interval (CI) for the risk of CIDP. Sex and disease-duration were included as covariates. By February-2017, 360 patients were enrolled, with complete data on 340 patients for antecedent events and comorbidities and 295 patients and 273 controls for lifestyle habits. Ninety-two patients (27%) reported an antecedent event, mostly infection or vaccination (20%). One or more comorbidity were present in 71% of the patients including hypertension (35.5%), thyroid disorders (17%) and diabetes (12.6%) and in 53% influenced the choice of initial therapy. Exposure to toxic environmental agents (odds ratio [OR] = 2.55; 95% CI, 1.42-4.55), cigarette smoke (OR = 2.02; 95% CI, 1.4-2.93), and dietary supplements (OR = 1.97; 95% CI, 1.08-3.58) were associated with a higher risk of CIDP while rice consumption was associated with a reduced risk (OR = 0.47; 95% CI, 0.25-0.87). Concerning disease severity, more severely affected patients more frequently consumed raw-meat (OR = 2.19; 95% CI, 1.05-4.58) and white meat (OR = 1.65; 95% CI, 1.03-2.63), while rice (OR = 0.42; 95% CI, 0.20-0.92) and soft drink consumption (OR = 0.57; 95% CI, 0.36-0.93) and physical activity were associated with lower disability (OR = 0.47; 95% CI, 0.29-0.77). This study confirms that comorbidities are frequent in patients with CIDP and often influence the choice of initial therapy. In addition preliminary data show that toxic exposure and some lifestyle and dietary habits may influence the onset and progression of CIDP.

ASSESSMENT OF INDIVIDUAL RESPONSE TO INTRAVENOUS IMMUNOGLOBULIN USING DAILY HOME MONITORING OF HAND GRIP STRENGTH IN CHRONIC INFLAMMATORY NEUROPATHIES

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Although hand grip-strength is a validated outcome measure in chronic inflammatory neuropathies, it is uncertain what threshold of change indicates a clinically meaningful improvement in an individual patient, also known as the minimum clinically important difference (MCID). Sixteen patients with chronic inflammatory neuropathies (10 CIDP, 5 MMN) on regular long-term intravenous immunoglobulin (IVIg) measured their grip-strength using the Martin Vigorimeter at home daily from one IVIg treatment until the next (median 28 days), to assess objective improvement between hospital visits and estimate the most reliable threshold for treatment responsiveness ("treatment-related fluctuation"). Patients recorded daily their subjective impression of change in global health. Ten healthy controls measured their grip-strength daily for a similar time. We assessed various statistical methods to distinguish treatment-related fluctuations from superimposed apparently random daily fluctuations in grip-strength. We analysed grip-strength changes from baseline in the weaker hand, comparing MCID thresholds of 8 kPa and 14 kPa. We used the mean of three grip-strength values on each day, but results were similar using the maximum each day. Controls had large random fluctuations. Mean daily grip-strength deviated by ≥8 kPa from baseline in 9/10 controls on a median 25% of their measured days, and by ≥14 kPa in 3/10 controls on 14% of their measured days, but never deviated by ≥14 kPa for more than three consecutive days. In patients, grip-strength increased by ≥8 kPa above baseline in 11 (73%) patients, on a median 70% (range 23-100%) of their measured days. Grip-strength increased by ≥14 kPa in 7 (47%) patients, on 52% of their measured days (range 7-94%) and in all for at least four consecutive days. Patients reported subjective health improvement on 89% (range 28-100%) of days on which the grip increased ≥8 kPa, and in 90% (range 66-100%) of days on which the grip increased ≥14 kPa. Although some recent studies used 8 kPa as the MCID threshold for grip-strength, we show this cannot reliably distinguish real improvement from random fluctuations. We recommend a MCID of 14 kPa on at least four consecutive days as a more specific indicator of treatment response in an individual.

CONDUCTION BLOCKS AND PARESIS INDUCED BY PASSIVE TRANSFER OF ANTI-CONTACTIN-1 IGG OF PATIENTS WITH CIDP

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Autoantibodies against the paranodal protein contactin-1 have recently been described in patients with CIDP. In most patients, autoantibodies of the IgG4 subclass are predominant and are supposed to be pathogenic. The role of IgG3 anti-contactin-1 is so far unclear.
In the present study, IgG of three different patients, one with IgG3 anti-contactin-1, one with a low titer of IgG4 anti-contactin-1 and one with a high titer of IgG4 anti-contactin-1, and of controls were injected into the sciatic nerves of Lewis rats. Nerve conduction studies of the injected nerve and motor and sensory testing were performed before and after injection.
Conduction blocks and motor deficits were detectable in the two patients with high titers of IgG3 and IgG4, not in the patient with low titers. The percentage of conduction blocks was 83.3% in rats injected with IgG of the IgG3 patient and 35% in those injected with IgG4. Motor deficits were detectable in both patients with conduction blocks but were most apparent in the patient injected with IgG of the IgG3 patient. No differences in sensory testing were observed. Conduction blocks and motor deficits improved after five days and were normal after seven to eight days.
Our data give the first evidence of pathogenicity of IgG3 anti-contactin-1 autoantibodies, not only IgG4. IgG of the IgG3 patient induced a more severe clinical and electrophysiological phenotype compared to the IgG4 patient. Remarkably, this reflected the clinical phenotype of the patients, as the IgG3 patients showed an acute-onset of sensorimotor symptoms at the time of blood withdrawal whereas the IgG4 patient presented with a more chronic course of disease.

NODES OF RANVIER IN SKIN BIOPSIES OF PATIENTS WITH DIABETES MELLITUS

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Axoglial dysjunction and paranodal demyelination have been discussed as potential mechanisms of nerve fiber damage in diabetic neuropathy. Studies on human tissue are limited, as nerve biopsies are invasive and only rarely performed in patients with confirmed diabetic neuropathy. Skin biopsy has recently been suggested as a good tool to analyze paranodal and nodal changes of myelinated fibers. In the present study, we analyzed the paranodal and nodal region in myelinated fibers of skin biopsies of 35 patients with diabetic neuropathy, 17 patients with diabetes mellitus without neuropathy, and 30 normal controls. Immunofluorescence of skin sections with antibodies against Caspr, neurofascin, sodium channels and myelin basic protein was performed to assess paranodal/nodal architecture, segmental demyelination and myelinated nerve fibers. Staining with antibodies against protein gene product 9.5 was used to quantify unmyelinated nerve fibers. We found an increase of elongated Ranvier nodes and a dispersion of neurofascin at the distal leg in patients with diabetes mellitus with and without neuropathy and at the finger in patients with diabetic neuropathy. An increased dispersion of Caspr was only found in biopsies of the finger in patients with diabetic neuropathy. Our data show that skin biopsy is an appropriate tool to analyze nodes of Ranvier in patients with diabetes mellitus. Structural nodal changes are detectable in diabetic neuropathy, and even in diabetic patients without neuropathy.

EGOS DID NOT HAVE A GOOD CAPACITY TO PROGNOSIS IN GBS IN RIO GRANDE DO NORTE, BRAZIL

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The Erasmus GBS outcome score (EGOS) is a validated prognostic model that uses acute phase and easy-to-obtain clinical characteristics to determine outcome at 6 months in patients with GBS. This study aims to assess the validity of EGOS in Rio Grande do Norte, Brazil, and to compare with another European study. Data collected prospectively from a cohort of 324 patients with GBS of Rio Grande do Norte, Brazil, between June 1994 and August 2016, was assessed. Ninety patients were excluded for missing data or diagnoses of Miller Fisher Syndrome and atypical forms of GBS. To calculate the EGOS, the GBS disability score was assessed in the second week of disease and at 6 months. To compare this study with the European one in independent group proportions, we used the Student's t-test, being considered statistically significant p<0,005. The 234 patients included were divided in four groups based on EGOS. Thus, 21 patients had EGOS between 1 and 3; 89 had EGOS between 3.5 and 4.5; 93 had EGOS 5 and 31 had EGOS between 5.5 and 7. In the first, second, third and fourth group, 0 (0%), 3 (3.4%), 10 (10.8%) and 6 (19.4%) of the patients were unable to walk independently after six months of the disease, respectively. Overall, of the 234 patients analyzed, 19 (8.1%) had poor outcomes in this study. In the European paper, based on the same group division, 1 of 193 (0.5%), 16 of 226 (7%), 43 of 161 (27%) and 94 of 182 (52%) were unable to walk independently. Comparing both studies, the patients of this study were younger, more seriously ill in the first weeks and with more sensitive deficits. There were no difference relative to sex, cranial nerves deficits and presence of anti-gangliosides antibodies. Using the Student's t-test for ability to walk after 6 months according to EGOS stratification, we achieve in the first group p=0.1629; in the second p=0.0784; in the third p=0.0004; and in the fourth p<0.0001.The EGOS did not have a good capacity to predict the ability to walk after 6 months of GBS in Rio Grande do Norte, Brazil.

HIGH INCIDENCE OF GUILLAIN-BARRÉ SYNDROME AFTER ZIKA VIRUS INFECTION IN THE STATE RIO GRANDE DO NORTE, IN NORTHEAST BRAZIL

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Historically, Guillain-Barré syndrome (GBS) epidemics are rarely seen. Between 1994 and 2014, we treated and followed 264 cases of GBS in the state of Rio Grande do Norte with a yearly incidence of 0.3/100,000. No seasonality was observed. The mean age of the patients was 27 years (range, 1 – 83), with 50% of the cases younger than 20 years. Demyelinating variant was the most frequent subtype of GBS. In March 2015, the first report of autochthonous transmission of Zika Virus (ZIKV) was determined in Natal, Brazil. Later that month, we documented an increase in incidence of GBS in Natal, Brazil. The incidence in 2015 was of 0.69/100.000. Of the 38 cases of GBS diagnosed in 2015, 24 were diagnosed from March through May, which coincided with the outbreak of ZIKV in Natal, Brazil. Eighteen patients (75% of the 24 cases) had a history of rash and fever prior to onset of GBS symptoms, with the median age of 45 years (range, 15-69). The electroneuromyography studies of these 18 patients indicated that 16 (88.9%) had acute inflammatory demyelinating polyneuropathy, 1 (5.5%) had acute motor axonal neuropathy, and 1 (5.55%) was inconclusive. The mean time from onset of ZIKV infection symptoms to onset of the GBS were 7 days (range, 3-30). The mean time of NADIR was 7 days (ranged, 4-25). Cranial neuropathies were present in 12 patients (66.66%). Nine patients were bedridden (50%) and 3 (16.66%) required mechanical ventilation. The mean protein content of the central spinal fluid was 0.77 g/L, with the white blood cell count below 5/mm in all patients. They were all treated with intravenous IgEV. They all improved quickly. Anti-GM1 was negative in all patients. RT-PCR was negative for Dengue, Chikungunya and Zika. Serum MAC-ELISA IgM for ZIKA and Dengue was made in 11 patients and it had 100% of positivity. PRNT for Zika and Dengue had 100% positivity. In summary, we report a geographically and temporally defined cluster of GBS associated with an outbreak of acute rash in the state of Rio Grande do Norte, Brazil.

CAPILLARY DYSFUNCTION IN THE DEVELOPMENT OF DIABETIC PERIPHERAL NEUROPATHY IN ANIMAL MODELS

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As the prevalence of diabetes mellitus continues to increase worldwide, diabetic complications represent a growing burden to patients and society. Distal symmetrical polyneuropathy (DSP) is a common complication that affects up to 30% of diabetic patients. DSP reduces patient quality of life due to chronic pain, ulcerations, and may lead to lower extremity amputations. Despite its high prevalence, the mechanisms underlying diabetic DSP are poorly understood and several mechanisms are believed to play a role. We hypothesize that diabetic DSP arises from microvascular complications characteristic to diabetes. Specifically, capillary dysfunction - disturbances in capillary flow patterns – is a likely candidate to explain development of DSP, as it can limit oxygen and nutrient delivery to nervous tissue, causing nerve dysfunction and damage, and thus development of DSP. We will study this hypothesis utilizing the state-of-the-art blood flow imaging techniques to visualize and quantify endoneureal blood flow and then link these findings with measures of DSP (e.g. nerve conduction velocity; intra-epidermal nerve fibre density) in animal models. We will include several animal models of diabetic DSP caused by either type 1 or type 2 diabetes. Two photon microscopy and optical coherence tomography allow visualisation and quantification of capillary transit times and blood flow within peripheral nerves at high resolution. We hypothesise that changes in blood flow patterns and subsequent impairment of nutrient and oxygen delivery to nervous tissue precede the onset of diabetic DSP. If our experiments support this prediction, we will attempt to develop interventions that improve capillary blood flow to prevent or delay the development of DSP.

TWO CASES OF IVIG RESPONSIVE INFANTILE ONSET AXONAL POLYNEUROPATHY

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Axonal polyneuropathies are very heterogeneous group of diseases which are very rarely seen during infantile age. Some of them may be accompanied by developmental retardation, severe muscle weakness and progressive course. We aimed to present two cases of axonal sensorymotor neuropathy with infantile onset and atypical course. Our 1-year-old boy patient was admitted to our clinic for progressive gait loss since one month. He was the first offspring of consanguineous parents with normal prenatal and natal history. Electromyography revealed axonal sensorymotor polyneuropathy. Metabolic and cerebrospinal fluid (CSF) examinations for etiology were all normal. Brain and spinal magnetic resonance imaging (MRI) were normal. He had partial benefit from oral steroid treatment. In the course of disease along with four neuropathy attacks he had significant benefit from serial intravenous

immunoglobulin treatments in two years clinical course. A 6 month-old girl who is the first offspring of nonconsanguineous parents was admitted to the clinic for acute tetraparesis. Axial sensorymotor polyneuropathy was detected in the electromyography. Metabolic and cerebrospinal fluid (CSF) examinations were normal. She had three more acute polyneuropathy attacks during IVIG cessation period. Both patients revealed with serial immunoglobulin treatments but unresponsive to riboflavine treatment. We aimed to discuss our rarely seen and the pathogenesis is not completely understood cases' course. Serial IVIG treatment may be helpfull for such patients' treatment.

GENOTYPIC AND PHENOTYPIC PRESENTATION OF TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY (TTR-FAP) IN TURKEY

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Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominantly inherited disorder caused by mutations of the transthyretin (TTR) gene. The mutant amyloidogenic transthyretin protein causes the systemic accumulation of amyloid fibrils that result in organ dysfunction. TTR-associated FAP is a progressive and fatal disease, if left untreated, and should be considered in the differential diagnosis of any person presenting with a progressive polyneuropathy, particularly with accompanying autonomic involvement.
The clinical, electrophysiological, histopathological, and genetic characteristics of 21 patients from Turkey (6 female, 15 male) from eleven families with polyneuropathy and mutations in TTR were evaluated. Two patients had no family history of TTR-FAP and were considered as sporadic cases, and the remainders were familial cases displaying an autosomal dominant inheritance pattern. Sequence analysis of the TTR gene revealed five mutations (p.Val30Met, p.Glu89Gln, p.Gly53Glu, p.Glu54Gly and p.Gly47Glu). Most common mutation was p.Val30Met (in 6 unrelated families). Mean age at disease onset was 41.4±14.2 years (range 21–66 years). The most commonly reported initial complaint was paresthesia in the feet (asymmetric in three patients). Four patients (2 male) with the p.Glu89Gln mutation presented with carpal tunnel syndrome. Two patients with the p.Gly53Glu mutation showed episodes of dysarthria and hemiparesis, consistent with this genotype. Seven patients died during the follow-up period as a result of systemic involvement.
This study suggests that our cohort of TTR-FAP patients from Turkey exhibits clinical and genetic heterogeneity.

CUTANEOUS NERVE FIBER ANALYSIS AS A BIOMARKER IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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Effect of amyloid deposition on cutaneous nerves was assessed in subjects with pathogenic TTR variants and control subjects. Three groups of 20 subjects each including TTR-FAP patients, age/gender-matched healthy subjects and disease controls as well as 10 TTR mutation carriers without neuropathy (TTR-noPN) and 2 with AL-amyloid underwent neurological examination and 3mm skin biopsies. 50 micron sections were stained with anti-PGP9.5, anti-TTR and Congo red. Amyloid burden with ImageJ, intraepidermal (IENFD) sweat gland (SGNFD) and pilomotor densities (PMNFD) measured and correlations between amyloid burden, fiber subtype, Neuropathy Impairment Score-LL (NIS-LL) and NIS sensory subscore were evaluated. IENFD, SGNFD, and PMNFD were all significantly reduced in TTR-FAP patients vs. healthy controls while mutation carriers had intermediate reductions. Lower nerve fiber densities were associated with NIS-LL ($p<0.001$). Congo red staining revealed brilliant red amyloid deposits with apple-green birefringence within dermal collagen, sweat glands, and arrector pili muscles. Amyloid infiltration was observed in the endoneurium and perineurium of small fiber sensory and autonomic nerves that innervate sweat glands and arrector pili muscles. Cutaneous amyloid deposition was detected in 70% of TTR-FAP and not in healthy or disease controls subjects. Both AL and 2/10 TTR-noPN subjects were Congo red positive. Amyloid burden was inversely correlated with IENF ($p<0.001$, $r=-0.63$) SGNF ($p<0.001$, $r=-0.67$), PMNF ($p=0.005$, $r=-0.50$) distal leg densities, and correlated with NIS-LL ($p=0.001$, $r=0.57$) and NIS sensory subscore ($p=0.004$, $r=0.54$). Wild-type TTR staining was less prominent in pathogenic TTR carriers. The diagnostic sensitivity and specificity to detect amyloid in skin were 70% and 100% in TTR-FAP. The repeat measurement of the amyloid burden from the same section with ImageJ was $r2=0.81$, $p<0.0001$ and different sections from the same biopsy was $r2=0.91$ and $p<0.01$. We conclude that endoneurial amyloid contributes to sensory and autonomic nerve injury. Amyloid burden correlated strongly with sensory/autonomic axon densities and NIS-LL. Skin punches offer a

convenient alternative to establishing a tissue diagnosis. Amyloid burden is an attractive biomarker marker for TTR-FAP and treatment effect.
The study was supported through a grant from Pfizer.

OBESITY ATTENUATES EPIDERMAL NERVE FIBERS IN THE DISTAL LIMB

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We investigated differences of unmyelinated sensory nerve fibers in the distal limb among 45 healthy-weight subjects (BMI < 25kg/m2) and 72 overweight/obese subjects (BMI ≥ 25kg/m2), aged 20-69 years. Subjects underwent neurological examination and 3mm skin punches from distal leg (DL), thigh (DT), and proximal thigh (PT) sites, from which 50 micron sections were stained with anti-PGP9.5 antibody; intraepidermal nerve fiber density (IENFD; fibers/mm) and epidermal thickness were assessed. A second DL biopsy was processed for electron microscopic examination and both thick and thin sections were examined for ultrastructural changes. Multivariable linear regression models were used to assess the effect of age, gender, height and weight. After controlling for height, age, and obesity, females were found to have lower distal leg IENFD (-2.6; p=0.02). Increasing age and height were significantly associated with decreasing DL IENFD, with decreases of -1.6 fibers/mm per 10 years (p<.001) and -2.55 fibers/mm per 10cm (p<0.001), respectively. Even after controlling for height, being overweight/obese was associated with reduced DL IENFD, with 2.5 fibers/mm lower DL ENFD than healthy-weight individuals (p=.01). These findings remained consistent across distal thigh and proximal thigh ENFD, though not all associations remained significant. The epidermis was thicker in obese subjects across the lower limb, most pronounced at the distal leg (μm, mean± SD, Healthy-DL:101±14.76, DT: 99.0 ± 10.3, PT: 107.7±12.2, Obese- DL:129.1± 48.3, DT:117± 33.0, PT:116.4±20.2). Under EM very few intact dermal nerve bundles were identified at the proximal thigh sites. The atrophic and degenerating axons were seen with perineurial infiltration by dense collagen in obsess/overweight subjects but not age/gender matched controls. Obesity further accelerates attenuation of epidermal nerve fibers across the lower limb even after controlling for other associated factors.

AXONAL NEUROPATHIES DUE TO MUTATIONS IN SMALL HEAT SHOCK PROTEINS: CLINICAL, GENETIC AND FUNCTIONAL INSIGHTS INTO NOVEL MUTATIONS.

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In this study, we describe the phenotypic spectrum of distal hereditary motor neuropathy caused by mutations in the small heat shock proteins HSPB1 and HSPB8 and investigate the functional consequences of newly discovered variants. Among 510 unrelated patients with distal motor neuropathy, we identified mutations in HSPB1 (28 index patients/510; 5.5%) and HSPB8 (4 index patients/510; 0.8%) genes. Patients have slowly progressive distal (100%) and proximal (13%) weakness in lower limbs, mild lower limbs sensory involvement (31%), foot deformities (73%), progressive distal upper limb weakness (29%), mildly raised serum creatine kinase levels (100%) and central nervous system involvement (9%). We found a broad range of disease onset with some patients presenting with foot drop at the age of 5 years, and others presenting symptoms only after 60 years. Disease progression was slow in all patients, and even with a disease duration of more than 40 years patients were still able to walk. None of our patients were wheelchair dependent. Muscle pathology, nerve pathology and electrophysiology showed in all cases a slowly progressive, mostly symmetrical and predominantly distal motor axonal neuropathy. Mild sensory involvement was observed upon nerve conduction studies, mostly the lower limbs, in 42% of cases. We identified 12 HSPB1 and 4 HSPB8 mutations, including respectively 5 and 3 not previously reported. Transmission was either dominant (78%), recessive (3%) or *de novo* (19%). Three missense mutations in HSPB1 (Pro7Ser, Gly53Asp, Gln128Arg) cause hyperphosphorylation of neurofilaments, while the C-terminal mutant Ser187Leu triggers protein aggregation. Two frameshift mutations (Leu58fs, Ala61fs) create a premature stop codon leading to proteasomal degradation. Two mutations in HSPB8 (Lys141Met/Asn) exhibited increased binding to Bag3. We demonstrate that HSPB1 and HSPB8 mutations are a major cause of inherited motor axonal neuropathy. Mutations lead to diverse functional outcomes further demonstrating the pleotropic character of small heat shock proteins.

INTERNATIONAL STANDARD FOR CIDP REGISTRY AND BIOBANK, RESULTS OF THE 231ST ENMC CONSENSUS MEETING

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Although chronic inflammatory demyelinating polyneuropathy (CIDP) is a treatable neuropathy further research is urgently needed to define the diagnostic clinical and electrophysiological boundaries of CIDP and its subtypes, and to define the role of biomarkers in supporting the diagnosis, monitoring disease activity and predicting response to treatment and outcome. In recent years, several national registries and biobanks have been developed to enable systematic data collection in CIDP. An international registry with large number of patients is needed to allow answering many important questions and develop validated prognostic models to predict outcome in individual patients with CIDP. At the Inflammatory Neuropathy Consortium (INC) Meeting in 2016, the INC members agreed that a European Neuromuscular Center (ENMC) workshop would be the ideal setting to reach a consensus on the infrastructure of database and biobanks. The 231st ENMC Workshop will take place on May 12-14, 2017 with participants representing 12 different countries. Primary objective of the workshop is to reach a consensus on inclusion and exclusion criteria, core sets and recommended sets of clinical data, diagnostic data and follow-up points and a manual of operations for collection of biomaterials. A secondary objective is to construct an infrastructure to allow sharing data between different databases and biomaterials. Conclusions of the consensus meeting and outline of further perspectives will be presented at the Peripheral Nerve Society Meeting in 2017.

DEVELOPMENT AND PILOT TESTING OF A FUNCTIONAL OUTCOME MEASURE FOR ADULTS WITH CHARCOT MARIE TOOTH NEUROPATHY (CMT-FOM)

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Clinical outcome assessments that measure functional ability are important endpoints for clinical trials. Dr. Burns has led the development/validation of a functional outcome assessment (CMTPedS) for individuals with Charcot Marie Tooth Disease (CMT) ages 3-20 years in the INC RDCRN. The CMTPedS is reliable and sensitive to change. However a validated Functional Outcome Measure (FOM) for adults with CMT is needed. Our data in 18-21 year-olds indicated that the CMTPedS could be modified for adult use. However, some items of the CMTPedS (e.g. balance beam and jumping) have floor effects in adults with CMT. We have developed an adult CMT-FOM modeled on the CMTPedS, and refined based on literature review, patient interviews, a large-scale CMT patient survey and expert opinion. The CMT-FOM is a performance-based Scale comprising 13 items that are combined to form a composite score to quantify functional ability of adults with CMT. The CMT-FOM shares 9 items with the CMTPedS. Four items were added to measure functional abilities relevant to adults (sit to stand, 10 meter walk/run, stair climb, and timed up and go test). The CMT-FOM scoring mirrors the CMTPedS. To generate a score ranging from 0-52, raw item scores are converted to z scores, based on age- and sex-matched normative reference values form the 1000 Norms Project and categorized to a 0–4 Likert along a continuum of impairment levels. We have conducted a pilot study of the CMT-FOM in adults with CMT1A (9 male, 12 female, age 39.7 ± 16.1 yrs) of differing severity (CMT Exam score (CMTES) range 1-20). The CMT-FOM is feasible, individuals were able to complete all items, and takes 35 minutes to perform. The mean CMT-FOM score was 22.0 ± 8.2 (range 11-37). Concurrent validity of the CMT-FOM is supported by an association with the CMTES (r = 0.51). The overall score did not demonstrate floor or ceiling effects. In summary the adult CMT-FOM is well-tolerated and captures upper and lower limb strength, dexterity, balance, speed, ambulation and endurance. The CMT-FOM requires validation in a large longitudinal cohort, prior to application in clinical trials.

FUNCTIONAL IMPLICATIONS OF HAND IMPAIRMENT IN PEDIATRIC CHARCOT-MARIE-TOOTH

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CMT is associated with progressive impairment of the hands. Reducing this impairment by treating children who are in the early stages of the disease is crucial. Studies assessing measures of CMT hand function in children and their associations with patient-reported outcomes are lacking. We analyzed the upper extremity items from the CMT Pediatric Scale (CMTPedS) and Pediatric CMT Quality of Life Scale (pCMT-QOL) in 179 children ages 8-18 years enrolled in the Inherited Neuropathies Consortium, to explore the relationships between measures of hand function (impairment, activity, and activities of daily living), and patient-reported outcomes. Weak grasp (67%), hand pain (30%), and tremor (40%) were prevalent impairments. Performance on activity level tasks, the Nine Hole Peg Test (9HPT) and Functional Dexterity Test (FDT), were impaired in 68% and 78% of the cases, respectively. Patients reported difficulty "sometimes" to "always" in opening a jar/lid (46%), zipping/buttoning (20%), writing (19%), carrying a plate without spilling food (17%) and putting on shoes (16%). Patients reporting tremor showed significant differences on the 9HPT (p=.04). Grip strength was shown to have a moderately significant correlation with performance on the FDT (r=.50; p<.0001). Stepwise multiple linear regression showed that grip strength (Beta=-.01; p<.001), hand pain (Beta=.86; p<.001) and FDT (Beta .01; p<.001) were predictive of ability to open a jar (adjusted R^2=.35; p<.001. Grip strength (Beta=-.003; p<.001), and FDT (Beta .01; p<.001) were predictive of ability to carry plate without spillage (adjusted R^2=.19; p<.001). Grip strength (Beta=-.003; p<.01), 9HPT (Beta=.01; p<.05) and FDT (Beta .01; p<.001) were predictive of ability to put on shoes (adjusted R^2=.23; p<.001). Hand pain (Beta=.39; p<.001) and FDT (Beta .02; p<.001) were predictive of ability to zip/button (adjusted R^2=.22; p<.001). Hand pain (Beta=.61; p<.001) and 9HPT (Beta .01; p<.05) were predictive of ability to use a pen/pencil (adjusted R^2=.09; p<.001). Children with CMT present with frequent limitations in ADL performance impacting QOL. The upper limb measures of the CMTPedS are associated with hand performance and interventions to improve grip strength and reduce pain should be investigated further with respect to their impact on improving function, and ultimately QOL.

MRI QUANTIFICATION OF INTRAMUSCULAR FAT ACCUMULATION IN CMT1A: FOUR YEAR FOLLOW UP DATA

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Responsive outcome measures are needed in Charcot-Marie-Tooth disease (CMT) to allow adequately powered clinical trials to test novel therapeutics. We have shown high responsiveness of MRI quantified intramuscular fat accumulation in calf muscles of CMT1A patients over 12 months. The aim of the present study was to assess the responsiveness and longitudinal validity of quantitative MRI over a 4 year follow-up period. We undertook two further sets of quantitative MRI, myometric and clinical assessments in the original MRC Centre CMT1A quantitative MRI cohort. MRI sequences included fat quantification using the 3 point Dixon fat-water separation method, T2 quantification and magnetisation transfer imaging. Of the 20 patients with genetically confirmed CMT1A were assessed at baseline (11 male, mean age 42.8 ± 13.9 years), 17 underwent repeat assessments a median on 12 months (data already published), 14 underwent repeat assessments at a median of 27 months, and 11 underwent a final assessment at a median of 49 months. The primary outcome measure currently being analysed is mean calf muscle fat fraction at a single axial slice a fixed distance distal to the knee joint. Results of this analysis and correlation with clinical measures will be presented at the Peripheral Nerve Society meeting.

ULNAR NERVE ENTRAPMENT IN MASSIVE MUSCLE FIBROSIS FOLLOWING INTRAMUSCULAR ANABOLIC STEROID INJECTIONS: A CASE REPORT

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The use of anabolic drugs by those who wish to increase lean body mass is widespread and not well supervised medically. A 36 years old man was referred for evaluation of a slowly progressive sensory and motor disturbance in the distribution of the left ulnar nerve. His symptoms began 10 months after repeated self-injections of anabolic steroids and vitamin E into the biceps and triceps brachii muscles bilaterally. His examination showed increased muscle mass of the injected muscles with a hard-rubbery consistency, atrophy and weakness of left interossei, mild weakness of the bilateral biceps brachii and sensory loss in an ulnar nerve distribution. Nerve conduction studies showed a left ulnar neuropathy with reduced motor and sensory response amplitudes and denervation in the left first dorsal interosseus, as well as mild myopathic changes with significantly reduced insertional activity in both biceps muscles. MRI of the soft tissues of the arms showed massive fibrosis and infiltration of fat in the arm muscles compressing the ulnar and median nerves on the left. Neurolysis of the left ulnar nerve was performed, and the ulnar nerve was found enclosed in a fibrotic mass throughout the entire length of the upper arm. The brachial artery and the median nerve were similarly enclosed in fibrotic tissue and were released. A biopsy of the affected muscles showed muscle necrosis and fibrosis. The patient was treated with physiotherapy and losartan with only mild improvement in the consistency of the muscles, but without clinical improvement in ulnar nerve function, and worsening of nerve conduction.

This case illustrates severe peripheral nerve damage due to entrapment in massive muscle fibrosis following improper intramuscular injection of anabolic steroids for cosmetic purposes.

PHENOTYPICAL AND GENOTYPICAL CROSSROADS BETWEEN INHERITED DISEASES OF NERVE AND MUSCLE: TWO EXAMPLES OF *VCP* AND *GNE* –RELATED DISORDERS.

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Inherited diseases of nerve and muscle may overlap phenotypically or coexists as facets of the same disorder. Two families whose probands were initially diagnosed with a lower motor-neuron (LMN) syndrome and a hereditary distal motor neuropathy (dHMN) turned out to represent a *VCP* (valosin-containing protein)-related syndrome and a *GNE* (UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase)-related "distal myopathy". Both conditions shared the presence of rimmed vacuoles (RV) in muscle biopsies. In family 1, the 61 year-old male proband had a LMN syndrome manifesting at age 58 years (wasting/weakness, cramps, fasciculations of thigh muscles, later involving the distal upper limbs). His 64 year-old brother had lower limb weakness and diffuse pain in bones/joints since age 54. The father was diagnosed with a "muscular dystrophy" thirteen years before dying a 76 years; by age 69 years he had developed a behavioural frontotemporal dementia (FTD). Electrodiagnosis (EDX) disclosed myopathic changes with ongoing denervation together with a mild sensory-motor axonal polyneuropathy in the proband, and a chronic sensory-motor axonal polyneuropathy in the brother. MRI showed fatty replacement of weakened muscles in both siblings and diffuse changes of bones consistent with Paget disease (PD) in the elder sibling. In family 2, a 32 year-old African woman was affected by weakness and wasting starting at the distal lower-limb muscles at age 23 years and soon progressed proximally; parents were not consanguineous and two sisters out of six siblings, deceased in their thirties for post-partum complications, had a similar disease. EDX mainly disclosed a neurogenic process with ongoing denervation. Muscle biopsies from the three family-1 patients and from the family-2 proband showed a myopathy with RV. Next-generation sequencing demonstrated a heterozygous c.277C>T change of *VCP* leading to a known pathogenic p.Arg93Cys substitution in all family-1 patients, and two compound heterozygous c.1441G>A and c.1561G>A changes of *GNE* in the family-2 proband leading to known p.Ala481Thr and p.Ala521Thr substitutions.
VCP is known to cause autosomal dominant Amyotrophic Lateral Sclerosis-14, Charcot-Marie-Tooth disease type 2Y or Inclusion Body Myopathy (IBM) with PD and FTD (IBMPFD); GNE causes the autosomal recessive Nonaka myopathy (alias IBM2). Both cases emphasize the clinical and neurophysiological heterogeneity of those disorders.

VARIED PATTERN ON PLEXUS MRI IN CIDP WITHOUT EFNS PNS DEFINITE ELECTROPHYSIOLOGICAL CRITERIA

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The diagnosis of CIDP is often challenging, especially when electrophysiological signs of demyelination are lacking. Plexus MRI has documented nerve abnormalities in small series of typical CIDP but its contribution in patients with no electrophysiological signs of demyelination remains to be proved. We report the results of plexus MRI in a serie of patients suspect of having CIDP without EFNS PNS definite electrophysiological criteria. We did a retrospective study of 44 patients consulting in Kremlin Bicetre and Pitié Salpétrière hospital. Lumbar or brachial plexus MRI (or both) were performed and we assessed nerve trophicity, T2-STIR signal intensity and gadolinium enhancement as well as the topography of abnormalities. A consensus diagnosis was made by a group of experts (based on clinical data and other supportive criteria) and allowed us to classified patients in "CIDP" or "other diagnosis". The practical contribution of plexus MRI to the diagnostic algorithm has been studied. Diagnosis of CIDP was made in 27 patients. MRI was abnormal in 67% of CIDP patients and showed nerve roots hypersignal/hypertrophy/enhancement in respectively 66.7/55.6/25.9% of patients. The pattern of abnormalities was often asymetrical (77.8%), diffuse (47.1%) or multifocal (41.2%). After unblinding, the MRI confirmed the diagnosis of experts in 61.4% of patients and changed the diagnosis in 20% of patients. Plexus MRI has shown to be useful in our serie to confirm the diagnosis of experts or to modify it in 9 patients (20%) . The "classical" pattern described in definite CIDP (diffuse nerve root hypertrophy and hypersignal) was documented in 30% of our CIDP patients whereas less typical pattern (focal or multifocal abnormalities, hypersignal without hypertrophy) was found in 37%. Plexus MRI seems usefull when facing patients suspected of having CIDP when electrophysiological criteria are not met: both symetrical diffuse or asymetrical multifocal patterns can be found and should be always correlated to the clinical examination and other supportive criteria. The specificity of such abnormalities remains to be studied.

MUTATIONS IN BAG3 CAUSE ADULT ONSET CHARCOT MARIE TOOTH DISEASE

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Mutations in Bcle-associated athanogene 3 (BAG3) have been shown to cause a distal myofibrillar myopathy and cardiomyopathy that can severely affect children or only affect adults depending upon the particular mutation. Children with severe cardiomyopathy and myopathy have also developed axonal peripheral neuropathy, consistent with the known localization of BAG3 in neurons as well as in muscle. We have identified two large autosomal dominant families with adult onset Charcot-Marie-Tooth disease (CMT2) with the identical novel missense mutation Pro209Ser, a codon previously shown to cause severe or mild myopathy depending on the amino acid substitution. These families expand the phenotypes caused by mutations in BAG3 to include CMT2 and provide an additional example of adult onset CMT2 that may previously have been diagnosed as chronic idiopathic axonal neuropathy (CIAP).

DUPLICATION OF MYELIN PROTEIN ZERO CAUSING EARLY ONSET CHARCOT MARIE TOOTH DISEASE TYPE 1B

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Myelin Protein Zero (MPZ), expressed only by myelinating Schwann cells, has sequence alterations that have previously been reported to cause demyelinating, intermediate, and axonal forms of Charcot Marie Tooth (CMT) disease. We describe a rare duplication in *MPZ* which is causing an early onset, demyelinating form of CMT in our patient. Patient was a product of a normal pregnancy and delivery. Early milestones were delayed. She began walking at 23 months of age. She was not able to keep up with her peers and was the slowest runner. She started wearing SMOs at 3 years of age and AFOs by 11 years of age. She was diagnosed with scoliosis at 2 years of age and started wearing a brace at 3 years. Her examination at 11 years of age showed that her FDI, APB, and ADM were all 4/5 bilaterally. Weakness in her lower extremities included 4/5 foot eversion and 3/5 great toe dorsi flexion. She had tight heel cords bilaterally. Pinprick sensation was reduced throughout in her upper and lower extremities and absent at her toes bilaterally. Vibration sensation with a Rydel tuning fork was absent at her toes and ankles and reduced at her knees and fingers. Nerve conduction studies were performed and revealed no responses in all sensory nerves tested with the exception of the radial nerve which had normal latency and mildly slowed conduction velocity (37 m/s). Prolonged latencies, demyelinating range slowing (between 13-16 m/s), and low CMAP amplitudes in almost all segments of the median and ulnar motor nerves were also observed. These findings were consistent with a hereditary sensorimotor demyelinating polyneuropathy. She was diffusely areflexic and her total CMT Pediatric Score (CMTPeds) was 34/44 which is in the severe range. Her CMT Neuropathy Score (CMTNS) was 14/36 in the moderate range. The duplication of *MPZ* has previously been identified as a rare cause of CMT1B.

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EXTREME VARIABILITY IN DISEASE SEVERITY IN A FAMILY WITH A NOVEL EGR2 MUTATION

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Mutations in *EGR2* cause a severe, demyelinating form of CMT, CMT1D. We describe a novel mutation in *EGR2* which led to extreme variability in severity in a family. Proband was a 12 year old girl who was the product of a normal pregnancy and delivery. Early milestones were on time. Problems with walking started at 2 years of age. At 2.5 she was unable to use stairs, run, or jump. At 4 she was wearing bilateral AFOs. By 5 she was using a wheelchair and started breathing assist at night. She lost arm lift but could still hold a pen. By 10 she could not ambulate independently and breathing assist was required day/night. She lost the ability to write and developed a head drop. By 12 years she could not sit up. On exam her head and neck muscles were 4/5. Upper limbs, deltoids, biceps, wrist ext/flex, finger ext, FDI, and ADM were 0/5 bilaterally. Triceps were 2/5; finger flexors and APB were 1/5 bilaterally. Lower limbs were 0/5 and she had contractures on the right. Sensory examination was normal. She was diffusely areflexic. NCVs were absent. Both the CMTNS and CMT Pediatric Score were severe at 26/36 and 42/44. Exome sequencing revealed a R381L variant in *EGR2* which was likely pathogenic. The probands' mother also had this mutation. She had no reported symptoms at the age of 33 with strength at 5/5 throughout with the exception of left foot eversion which was 4+/5 and great toe dorsi flexion which was 4-/5 bilaterally. Sensory exam showed a decrease of vibration and pinprick sensation at left toe. She had a normal gait, tandem gait and could toe walk, but not heel walk. She was diffusely areflexic. NCVs showed absent sensory responses. Motor NCVs showed her latencies were prolonged and velocities reduced (29-33 m/s). CMTNS was mild (5/36). Additional family members who had the R381L mutation were evaluated including maternal grandmother who was moderately impaired (19/36) and maternal aunt who was severe (26/36). No other mutations that could cause another known neuropathy or myopathy were identified and mitochondrial sequencing was normal.

Inherited Neuropathy Consortium is part of the NIH Rare Diseases Clinical Research Network (grant#1U54NS065712-01).

SARM1 DELETION AND WLDS ARE NEUROPROTECTIVE IN THREE MODELS OF CHEMOTHERAY INDUCED PEIRPHERAL NEUROPATHY

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Molecular mechanisms that underlie slow distal axonal degeneration seen in chemotherapy induced peripheral neuropathy (CIPN) are unclear. However, several identified molecular targets suggest shared mechanisms with Wallerian degeneration. Since spontaneous mutation in Wlds mice and genetic deletion of Sarm1 gene lead to slow Wallerian degeneration, we asked if Wlds or Sarm1 knockout (KO) mice are resistant to distal axonal degeneration induced by several chemotherapy agents. We chose chemotherapeutic drugs from 3 different classes of agents, paclitaxel (taxane), cisplatinum (platin-based drugs) and bertozomib (proteasome inhibitor), to model CIPN in mice. Primary outcome measure was evaluation of epidermal nerve fibers in the hind paw plantar footpads. Secondary outcome measures included thermal sensation and nerve conduction studies. Sarm1 KO mice were almost 100% protected against development of sensory neuropathy but the protection in Wlds mice was partial. This study confirms the pivotal role Sarm1 plays in mediating axonal degeneration and identifies inhibition of Sarm1 activity as a potential therapeutic target for prevention of CIPN.

LIMITED SCHWANN CELL DIFFERENTIATION AS A PROTECTIVE MECHANISM IN CMT1B NEUROPATHY WITH ACTIVATED UNFOLDED PROTEIN RESPONSE

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Myelin Protein Zero is the most abundant structural protein in myelin of the PNS. In humans, more than 200 mutations in P0 are associated with hereditary neuropathies. Deletion of serine 63 causes Charcot-Marie-Tooth (CMT) 1B disease in humans and a similar demyelinating neuropathy in mice (Wrabetz et al., 2006). P0S63del protein is misfolded and is retained in the ER where it gives rise to a dose-dependent Unfolded Protein Response (UPR) (Pennuto et al., 2008). The UPR results in the activation of transcriptional and translation control programs that reduce protein synthesis and increase the folding and degradative capacity of the cell. Usually, when this first response is not sufficient the cells may activate apoptosis resulting in cell death. However, in P0S63del Schwann cells there is no cell death suggesting that these cells may respond differently to chronic stress. Transcriptomic analysis performed on P0S63del nerves showed increased expression of transcription factors normally present only in the early phases of differentiation such as c-Jun, Sox2 and Id2 (D'Antonio et al. 2013). In order to understand the role of the expression of these factors in the peripheral nerve myelination we used ex vivo and in vivo approaches and we showed that Sox2 and Id2 act as negative regulators of myelination. These results suggest that the expression of Sox2 and Id2 may contribute to the hypomyelination observed in P0S63del mice. As such, we reasoned that their ablation could ameliorate the phenotype. Surprisingly, the ablation of these factors in the P0S63del mouse severely worsens the neuropathy bursting Schwann cell differentiation and increasing the expression of both P0 wild type and mutant allele with concomitant exacerbation of the UPR. This suggests that the overexpression of early differentiation factors in Schwann cell under chronic ER-stress is an adaptive mechanism that limits differentiation and reduces the expression of toxic proteins.

MODELLING THE PHARMACOKINETICS OF INTRAVENOUS IMMUNOGLOBULIN IN GUILLAIN-BARRÉ SYNDROME

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Intravenous immunoglobulin (IVIg) is the treatment of choice for the Guillain-Barré syndrome (GBS). The working mechanism of IVIg in GBS is undefined, but most likely all potential effects are dose dependent. The pharmacokinetics (PK) and pharmacodynamics (PD) of IVIg in GBS are highly variable between patients and a rapid consumption or clearance of IVIg is associated with poor recovery. In the current study we developed a model to predict the PK of a standard dosage of IVIg (0.4 g/kg for 5 consecutive days) in individual patients with GBS. Non-linear mixed-effects modelling (NONMEM) was used to construct a model based on a cohort of 177 GBS patients, with a total of 811 sequential serum IgG levels. The final model accurately describes the day to day increment in IgG levels during the 5-day course and the initial rapid fall and graduate decline to steady-state levels thereafter. We explored several potential covariates that improved the predictive capabilities and decreased the between-subject variation in the model. The model including these covariates were evaluated successfully (bootstrap analysis) and through numerous simulation studies each based on 1000 (simulated) GBS patients. In conclusion, a first accurate and robust NONMEM model for the PK/PD of standard IVIg treatment in GBS was developed. The model can be used to predict the PK in individual patients applying a few simple baseline characteristics. In addition, the effect of different treatment regimens of IVIg in GBS on a population PK/PD level can be simulated. This modeling technique is a new tool to optimize the PK in individual patients and the study design for new trials with IVIg in GBS.

ROLE OF L-PGDS IN SCIATIC NERVE REGENERATION AFTER INJURY

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Axonal Neuregulin 1 (NRG1) type III is an essential instructive signal for Peripheral Nervous System (PNS) myelination, as its expression determines whether axons are myelinated as well as the thickness of the myelin sheath. We recently demonstrated that gamma-secretase cleavage of NRG1 type III generates an axonal intracellular fragment, which translocates in the nucleus to upregulate the expression of the Prostaglandin D2 Synthase (L-PGDS) gene in neurons. L-PGDS catalyzes the conversion of prostaglandin H2 into prostaglandin D2 (PGD2). We also showed that specific inhibition of L-PGDS activity impairs *in vitro* myelination. Accordingly, myelin in L-PGDS null mice is noticeably thinner, thus indicating that L-PGDS is a new modulator of developmental PNS myelination. Previous studies have shown that prostaglandins are involved in the process of Wallerian Degeneration (WD) and axonal regeneration after injury. Thus, to determine whether L-PGDS and PGD2 could be important in PNS regeneration and remyelination, we performed sciatic nerve crush injury in 2 months old L-PGDS null and wild type control mice and we analysed nerves by morphologic, biochemical, histological and molecular approaches at different time points (T) after crush. We focused on three phases: degeneration (T3 – T7), axon regeneration (T14 - T21) and remyelination (T60). Our results indicate that in L-PGDS null mice the amount of myelin proteins synthesized after crush as well as the number of remyelinated fibers do not change, suggesting that L-PGDS might be dispensable for remyelination. However, we observed an increased number of macrophages in null nerves during regeneration (T14), possibly as a consequence of an increase in the Blood-Nerve Barrier (BNB) permeability, indicating potential alteration in the regeneration process in L-PGDS null mice. These results suggest that L-PGDS could have a different role in developmental PNS myelination and after injury. Whether other prostaglandins and synthases might compensate for L-PGDS activity is currently under investigation.

ENRICHEMENT OF CHITOSAN TUBES WITH SKELETAL MUSCLE FIBRES TO IMPROVE PERIPHERAL NERVE REGENERATION

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To repair nerve gaps following severe peripheral nerve injuries, chitosan tubes were proved to give good results, comparable with those obtained with nerve autografts, the gold standard technique.
To further improve peripheral nerve regeneration using chitosan tubes, a conduit enrichment strategy was developed using longitudinal skeletal muscle fibres, which have been previously shown to be good fillers in the “muscle in vein” experimental paradigm, where they played a trophic and a structural role.
To this aim, rat median nerve gaps were repaired using two different conduits: 10mm chitosan tubes filled with a longitudinal piece of *pectoralis major* muscle (“muscle in tube”) and hollow chitosan tubes. Samples were harvested at early time points (1, 7, 14, 28 days) for biomolecular and morphological analysis, and later (3 months) for stereological analysis. Autologous nerve grafts were used as gold standard positive control in the early time points.
Biomolecular analysis carried out on *in vitro* degenerating muscle and on “muscle in tube” at early time points show that the muscle produces high levels of soluble isoforms of Neuregulin1, a key factor for Schwann cell survival and activity, usually released by Schwann cells after nerve injury.
Functional assay and stereological analysis carried out on the distal part of regenerated nerve 3 months after nerve repair, show no significant differences in the regeneration outcome between hollow chitosan tube and “muscle in tube” groups.
Therefore, we conclude that for short gaps (≤10mm), both hollow chitosan tube and “muscle in tube” are good techniques to repair nerve defects and we suggest that the “muscle in tube”, which spontaneously releases Neuregulin1, might be a promising strategy to promote regeneration when the gap is longer or the repair is delayed in time.

SENSITIVITY TO CHANGE OF THE *CHARCOT-MARIE-TOOTH NEUROPATHY SCORE* (CMTNS) AND *OVERALL NEUROPATHY LIMITATION SCALE* (ONLS) IN A DATABASE OF FRENCH PATIENTS WITH CMT1A

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Charcot-Marie-Tooth disease Type 1A (CMT1A) is a rare disease belonging to a group of inherited, progressive, chronic motor and sensory peripheral

neuropathies. The *Charcot-Marie-Tooth Neuropathy Score* (CMTNS) (Shy et al., 2005) and the *Overall Neuropathy Limitations Scale* (ONLS) (Graham & Hughes, 2006) are considered as the main clinical scales for evaluating progression of disability associated with CMT. As CMT1A is a slowly progressive neurodegenerative disease, the choice of endpoints and their ability to monitor small changes over time remain a major concern for clinical drug development. With this in mind, we studied a cohort of 225 French CMT1A patients with a follow-up ranging from 3 months to 8.5 years resulting from the merge of two multicentre clinical trials (Micallef et al., 2009; Attarian et al., 2014) and a non-interventional study (unpublished). The sensitivity to change of both CMTNS and ONLS were assessed using a mixed effect model estimating annual progression with time in years, CMTNS or ONLS baseline value as covariates, study centre as a fixed factor and patients as a random effect to account for the repeated measures. Disease progression was estimated to be +0.13 points per year on the CMTNS (p = 0.0037) and +0.052 points per year on the ONLS (p = $1.1x10^{-5}$), both corresponding to a deterioration of impairment and disability. While both endpoints have similar and favourable properties, our set of observations led us to conclude that the ONLS could be more promising to monitor disease progression in CMT1A.

CLINICAL AND MAGNETIC RESONANCE IMAGING FEATURES OF THREE NOVEL MUTATIONS IN THE *BICD2* GENE

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Mutations in the *BICD2* gene are a cause of dominant spinal muscular atrophy, lower extremity predominant (SMALED). We report six patients belonging to three Spanish families who carry three different novel mutations in the *BICD2* gene. We describe clinical, electrophysiological and Magnetic Resonance Imaging (MRI) data. We provide results of muscle biopsy of one patient and skin biopsy for the study of Epidermal Nerve Fiber Density (ENFD) of other two patients. Genetic diagnosed was reached using a gene panel for genetic testing of CMT and dHMN. Three novel mutations in the *BICD2* gene that segregated with the disease were detected: p.Val485Gly; p.Tyr557His and p.S681L. The most frequent clinical phenotype consisted of mild weakness in proximal muscles of lower limbs combined with foot deformities. One patient had prominent sensory symptoms and abnormalities on sensory examination. Other two patients had minor sensory abnormalities on examination. In one patient sensory and motor nerve action potentials were reduced, in the rest of patients electrophysiological studies showed normal motor and sensory nerve responses, with chronic denervation predominantly in muscles of lower limbs. MRI studies at the level of tight and calf were performed in all patients. The most affected muscles were rectus femoris, vastus lateralis and medial gastrocnemius. MRI studies at the level of feet were obtained from five patients and showed that there was not fatty infiltration in intrinsic foot muscles. MRI at the level of pelvis muscles performed in four patients showed marked fatty infiltration of gluteus medius muscle in two of them. Muscle biopsy performed in one patient showed myopathic features. Skin biopsy was performed in two patients of the same family. In the older patient, who had minor sensory abnormalities on examination, there was a marked reduction of ENFD that followed a length-dependent pattern. In conclusion, we report three new pathogenic mutations in the *BICD2* gene. In our study we include MRI findings at the level of pelvis and feet, which allow us to better define the pattern of muscle involvement related with this gene. Our results also raise the subject of a possible sensory involvement in the disease.

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PILOT STUDY OF CLINICAL SEVERITY SCORE FOR HEREDITARY NEUROPATHY WIITH LIABILITY TO PRESSURE PALSIES

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Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) is an autosomal dominant disorder that usually results from deletions in the *PMP-22* gene. The neuropathy is unique in that it manifests with recurrent mono-neuropathies at common sites of compression. While spontaneous recovery from episodes of nerve injury usually occurs, it is often incomplete, and over time patients may develop a length dependent polyneuropathy. Given the relapsing/remitting nature of HNPP symptoms, standard clinical scores, such as the CMT Neuropathy Score, are not effective at capturing the severity or progression of the disease. A specific tool is therefore needed for measuring clinical severity of HNPP in preparation for emerging clinical trials. In the current study, we evaluate a new pilot measure, the HNPP Severity Score (HNPPS). The score is composed of 32 patient reported questions addressing current and prior sensory and motor symptoms, and the impact of symptoms on quality of life, followed by 7 items based on a motor examination. Total scores vary from 0-85, with higher scores indicating increased disease severity. In this study, the HNPPS was administered to 41 patients with genetically confirmed HNPP at the UCL Institute of Neurology. Subjects included 21 males and 20 females with a mean age of 41 years (+/-15, range 16-70). The mean HNPPS was 24.4 points (+/-12.4, range 3-56) and the data did not demonstrate major skew. The Cronbach alpha for the HNPPS was 0.90,

and items based on the physical examination showed the least variability. A modest correlation was observed between the HNPPS and the CMT examination scores (Pearson correlation 0.57, CI 0.3-0.74). We conclude that the HNPPS may be a useful measure of clinical severity in HNPP, and should be refined in larger patient cohorts.

DISEASE PROGRESSION IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: A LONGITUDINAL STUDY USING RASCH ANALYSIS-BASED WEIGHTED CMT NEUROPATHY SCORES

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The most common of the hereditary neuropathies (HN) is CMT1A, an autosomal dominant demyelinating neuropathy that results from duplications in the *PMP-22* gene. Recent advances in defining the pathomechanisms of the disease have led to an increasing number of potential therapies; however, the absence of reliable natural history data and the paucity of sensitive clinical outcome measures have been barriers to effective clinical trials. The Charcot Marie Tooth Neuropathy Score (CMTNS) was developed to quantify impairment and measure progression in HN. It was observed that while the score discriminates well between mildly and severely impaired patients, it tends to cluster together patients in the middle range of severity. To improve the score's sensitivity, Rasch analysis-based weighted category responses were developed. We report a longitudinal study of weighted CMTNS and CMT examination scores (CMTES) over a three-year time frame in patients with CMT1A. Baseline, one year, two year and three year wCMTNSv2/wCMTESv2 scores were available for 434/730, 49/236, 31/148 and 17/74 patients respectively. Mean wCMTNS (SD)/wCMTES (SD) scores were as follows: 19.2(7.2)/12.7(6.5) at baseline, 19.0 (7.1)/13.0(6.0) at one year, 22.1 (7.6)/13.7 (6.3) at two years and 22.7 (7.6)/14.1(6.8) at three years. A mixed regression model showed significant change in wCMTNS and wCMTES at 2 years (mean change from baseline at 2 years was 1.7 points (p=.003) for wCMTNS and 0.59 points (p=.02) for wCMTES. Significant change as compared to baseline was also seen at 3 years (mean change from baseline 2.0 points (p=0.02) for wCMTNS and 0.69 points (p=0.04) for wCMTES. We conclude that weighted CMTNSv2 scores show change over the first three years of the Inherited Neuropathies Consortium natural history study and are a helpful measure of progression in CMT1A.

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL EVALUATING THE SAFETY AND EFFICACY OF L-SERINE IN SUBJECTS WITH HEREDITARY SENSORY AND AUTONOMIC NEUROPATHY TYPE 1 (HSAN1)

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HSAN1 is an autosomal dominant, severe sensory motor polyneuropathy caused by mutations to serine palmitoyl-CoA transferase. Mutations shift the substrate preference from serine to alanine leading to formation of neurotoxic 1-deoxysphingolipids (1-deoxySL). Treatment with high-dose L-serine has been shown to reduce 1-deoxySL accumulation and improve neuropathy in transgenic HSAN1 mice. We report a two-year, delayed-start, placebo-controlled clinical trial evaluating the safety and efficacy of oral L-serine in HSAN1. Eighteen HSAN1 subjects were equally randomized to L-serine (400 mg/kg/d) or placebo for 1 year. At 48-weeks, the placebo group crossed-over and all participants took open-label L-serine for one additional year. Sixteen subjects completed their 96-week visit, and no serious adverse events related to L-serine were reported. Participants randomized to L-serine experienced a decline in Charcot Marie Tooth Neuropathy Scores (CMTNS) over 1 year relative to placebo (-1.8 units, 95% CI -3.3 to -0.3, p = 0.02). Both groups improved in the second year of the study, with a diminished difference in CMTNS at 96 weeks (-1.45 units, 95% CI -3.7 to 0.81, p=0.20). Skin biopsies from the distal leg site were largely devoid of intra-epidermal nerve fibers (IENF), but at 1 year, a greater increase in IENF density was seen in participants on L-serine versus those on placebo (median change of 8 vs. 0 fibers/μm^2, p=0.014). 1-deoxySL levels declined among participants on L-serine versus those on placebo after one year of treatment (60% decrease in deoxysphinganine vs. 9% increase on placebo, p < 0.001), and placebo participants experienced similar declines in 1-deoxySL levels after crossing over to L-serine. We conclude that L-serine is a safe and potentially efficacious treatment for HSAN1.

MALIGNANCY IN GUILLAIN-BARRE SYNDROME: A TWELVE-YEAR SINGLE-CENTER STUDY

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The relationship between Guillain-Barré syndrome (GBS) and malignancy is uncertain. Under the diagnostic criteria of Paraneoplastic Neurological Syndrome (PNS) by Euronetwork, 2004, neuropathy with no definite onconeural antibodies identified due to GBS has been classified as "non-classical" paraneoplastic disorder. We retrospectively analyzed data of 118 consecutive patients admitted with GBS

from Birmingham, U.K. (2001−2012) to calculate the relative cancer risk using different definitions and determined characteristics of malignancy-associated GBS. Patients were classified according to 2 definitions: 1) all cases of malignancies excluding preceding diagnoses >1 year before GBS and with no evidence of malignant disease activity at the time of GBS diagnosis, and 2) malignancies diagnosed >2 years post-GBS onset as per PNS criteria. Total number of GBS patients with malignancy was 10 (9.2%). A total of 6 patients (5.5%) fulfilled requirements for inclusion as malignancy-associated GBS as per existing criteria for PNS. Associated malignancy consisted of angioimmunoblastic T-cell lymphoma (1), poorly differentiated squamous cell carcinoma of nasal septum (1), gastric adenocarcinoma (1), hepatocellular carcinoma due to hepatitis B (1), rectal carcinoma with liver metastasis (1) and myelodysplastic syndrome (1). Malignancy was globally commoner in our GBS cohort compared to the general population (odds ratio: 2.08; CI: 1.06–3.71; p = 0.036). However, this was unconfirmed if paraneoplastic criteria were applied. GBS patients with cancer were significantly more likely to be older (p = 0.043), hyponatremic (p = 0.037) and demonstrate more electrophysiological axonal loss (p < 0.05). Cerebrospinal fluid (CSF) protein levels were lower in the malignancy group (p=0.002) and neurological improvement was less likely (p=0.023). In-patient mortality was significantly higher in patients with malignancy (p < 0.01). None of the patients in the malignancy group had positive anti-ganglioside antibodies or anti-neuronal antibodies (anti-Hu, Yo, Ri, CRMP5). We conclude global cancer risk is higher in GBS than in the general population, although definition-dependent. Application of the strict published criteria for paraneoplastic syndrome reduced the number of cases and suggested absence of a link. Malignancy requires consideration in elderly, hyponatremic subjects with normal CSF protein, severe electrophysiological axonal loss who fail to improve post-treatment.

QUALITY OF LIFE IN ANTI-MAG NEUROPATHY: EVALUATION OF DETERMINANTS IN A MULTICENTRE EUROPEAN SETTING

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Anti-myelin associated glycoprotein antibody (Anti-MAG) neuropathy is a slowly progressive neuropathy resulting in disability through distal sensory more than motor deficits and tremor. There are currently no evidence-based treatments for anti-MAG neuropathy and the effect of the disease on quality of life (QoL) in this patient population is unknown. Our objective was to assess determinants of QoL in patients with anti-MAG neuropathy. The SF-36 questionnaire was assessed in 55 patients, from Marseille, Angers (France) and Birmingham (United Kingdom). Routine clinical evaluations included MRC sum score, INCAT sensory score, Inflammatory Rasch built Overall Disability Score (I-RODS), ataxia score, Jamar grip dynamometry, timed 10 meter-walk, Neuropathic Pain Symptom Inventory (NPSI) score, and Fatigue Severity Score (FSS). There were 38 males and 17 females. Mean age was 71.5 years (SD: 10.3 years). Mean disease duration was 7.4 years (S.D.: 5.9 years). There were no significant differences between the French and U.K. cohorts in terms of gender distribution, age, disease duration, anti-MAG antibody titre. All physical assessments, including MRC sum score (p=0.87), Jamar grip dynamometry (p=0.54), ONLS (p=0.11), IRODS (p=0.66), INCAT sensory score (p=0.60), 10-meter timed walk (p=0.46), ataxia score (p=0.65), tremor score (p=0.25), were comparable. Prevalence and/or severity of pain (p=0.55), fatigue (p=0.86), restless legs syndrome (p=1) and cramps (p=0.54) were also similar. Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF36 questionnaire were significantly lower than in reported normal subjects of both countries (p<0.001). All SF-36 QoL domains correlated with I-RODS, except MCS for which significance was however approached (p=0.056). PCS correlated with MRC sum score, ataxia score, timed 10 m-walk, tremor, Jamar grip dynamometry, NPSI pain score, FSS and level of social support. MCS correlated exclusively with FSS and level of social support. In multivariate regression, PCS was associated independently with I-RODS (p<0.001) and NPSI pain score (p=0.011), whereas MCS was associated independently with FSS (p=0.022). QoL is accurately predicted in anti-MAG neuropathy by the I-RODS and FSS, lending support to their use in clinical and research settings. Effective measures to improve QoL should include tremor and neuropathic pain treatment, fatigue management and improved social support.

OPTIMIZING ELECTRODIAGNOSTICS FOR GUILLAIN-BARRE SYNDROME: CLUES FROM CLINICAL PRACTICE

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The electrophysiological diagnosis of Guillain-Barré syndrome (GBS) is dependent on a number of abnormalities affecting different parameters in peripheral nerves on nerve conduction studies (NCS). Diagnostic sensitivity varies with different electrodiagnostic criteria, practices as well as extensiveness of nerve study. However, the most efficient method of performing electrophysiology for Guillain-Barré syndrome (GBS) is unknown. We retrospectively analyzed electrophysiological data of 97 consecutive GBS patients from Birmingham, UK (2001-2012), studied ≤ 3 weeks post-onset. We first identify abnormal nerves from various regions which produced GBS electrodiagnosis using the recently described criteria by Rajabally et al. We subsequently used pre-established hypothetical nerve conduction study protocols to determine the potential optimal method of achieving electrodiagnosis. We found the sensitivity of electrophysiology for each GBS subtype was dependent on the upper and lower limb nerves tested. In acute inflammatory demyelinating polyneuropathy (AIDP), abnormalities were predominant in the arms, whereas leg abnormalities predominated in axonal GBS. In AIDP, the most common abnormal parameters were distal motor latency (46.4%) and conduction block (46.7%), and the most frequently affected nerve was the median (40.1%). Prolonged F-waves were present in 32% and F-waves were absent in 29%. MCV was the least frequently abnormal (23.7%) with demyelinating range slowing, significantly lower than CB or DML prolongation ($p<0.001$ in both cases). In axonal GBS, reduced motor amplitudes (38.1%) and conduction block (35.1%) were the most common parameters, and the most frequently abnormal nerve was the tibial (46.9%). F-waves were absent in 32.1%. 12.5% of all motor nerves were unexcitable, significantly more common in lower limb nerves compared to upper limb nerves ($p=0.03$). On comparison of different hypothetical NCS protocols (2 unilateral protocols with 2 nerves, 2 with 3 nerves as well as the protocols with 4-nerves and with exclusive bilateral upper limb and lower limb testing), unilateral 4-nerve (median, ulnar, common peroneal and tibial) testing produced the highest diagnostic sensitivity for both AIDP (95.6%) and axonal (91.1%) GBS. Electrodiagnostic sensitivity in GBS is thus dependent on nerves tested and parameters considered. Each subtype preferentially involves specific nerves and parameters. These findings may help per-procedure interpretation, improve electrodiagnostic sensitivity, and reduce patient discomfort.

ANTI-GANGLIOSIDE COMPLEX ANTIBODIES IN CHRONIC IMMUNE-MEDIATED NEUROPATHIES

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Recently, IgG anti-ganglioside complex (GSCs) antibodies have been reported in patients with Guillain-Barré and Miller Fisher syndrome. Some researchers (Nobile-Orazio et al., 2010) reported IgM anti-GSCs antibodies in multifocal motor neuropathy (MMN) and other chronic immune-mediated neuropathies. In ten of eleven MMN patients with anti-GM1 antibody, there was a decreased reactivity to GM1/GD1a compared to single antigen GM1. Similarly, in one of two chronic inflammatory degenerative polyradiculoneuropathy (CIDP) patient with anti-GM1 antibody, there was a decreased reactivity to GM1/GM2, GM1/GD1a, GM1/GD1b, GM1/GT1b compared to GM1. These relationships were defined negative interaction. In one CIDP with anti-GD1b antibody, anti-GM1/GT1b and -GM2/GT1b reactivity increased although GM1 and GM2 were negative (positive interaction). In japan, on the other hand, this correlation remains unclear. Sera were investigated from one MMN patient (38 y/o male) with anti-GM1, and anti-GD1a antibody, one CIDP patient (72 y/o female) with anti-GM1, and one subacute sensory motor polyradiculoneuropathy (70y/o male) with anti-GD1b, and anti-GQ1b. IgM antibodies to GSCs GM1/GD1a were tested with a mixture of GM1 and GD1a (each 5 pmol/well) as antigen. Anti-GM1/GD1a antibodies were judged to have positive interactions when the optical density was 0.5 greater than the sum of the antibodies against individual GM1 and GD1a, and negative interactions when the optical density was 50% or less compared to the antibodies against individual GM1 or GD1a. Antibodies to at least one combination of two of the six gangliosides (GM1, GM2, GD1a, GD1b, GT1b, and GQ1b) were similarly tested and judged for positive or negative interactions. In one MMN, anti-GM1/GD1a had negative interactions. In one CIDP, anti-GM1/GD1a, and anti-GM1/GQ1b had negative interactions. In one subacute sensory motor polyradiculoneuropathy, various anti-GSCs antibodies including GD1b or GQ1b had negative interactions. In the CIDP patient mentioned above, anti-GM1/GT1b or anti- GM2/GT1b had no positive interactions. The relationship between this attenuated reactivity presumably driven by adjacent gangliosides and the mechanism of chronic immune-mediated neuropathies needs to be clarified.

RALGTPASES CONTROL SCHWANN CELL'S REPAIR FUNCTION AFTER NERVE INJURY BY CONTROLLING LAMELLIPODIA FORMATION.

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Schwann cells (SCs) are the myelinating cells in peripheral nerve system and are important for normal peripheral nerve development and repair. RALA and RALB are small GTPases that have been implicated in neural tube closure, neurite branching and have been described as upstream effectors of proteins involved in cell migration and membrane dynamics. Due to their potential role in SC function here we investigated, by genetic ablation in transgenic animals of one or both GTPases, their importance in SC function in adulthood and in nerve repair. We showed that Ral GTPases are dispensable for SC function in the naïve state. However Ral signalling (provided by RalA or RalB) is required for effective remyelination of axons following nerve injury. Moreover, absent Ral signalling produced defects in axon reinnervation of distal organs and a delay in motor function recovery after nerve injury. We also studied the Ral dependent cellular mechanisms that may be responsible for impaired SC remyelination and noted abnormal SC lamellipodia formation that prevent normal axial and radial axon remyelination. This work demonstrates for the first time a novel mechanism for RalGTPases that controls SC lamellipodia formation and their importance in normal SC function during peripheral nerve repair.

CHARACTERIZATION OF A TRANSGENIC MOUSE MODEL OVEREXPRESSING TNF ALPHA IN MYELINATING SCHWANN CELLS

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Tumor Necrosis Factor (TNF) alpha has been implicated in the pathogenesis of diabetic peripheral neuropathy (DPN), among other inflammatory demyelinating diseases and neuropathic pain. TNF alpha is a pro-inflammatory cytokine that can act at several stages in the demyelination process. It is produced by Schwann cells (Scs) in the peripheral nervous system (PNS) after nerve injury and released into the local environment to attract and activate macrophages at the site of injury, contributing to Wallerian degeneration. In vivo studies demonstrated a local inflammation in the sciatic nerve of rats after injection of TNF alpha, followed by demyelination and axonal degeneration. Furthermore, the application of TNF alpha resulted in acute mechanical hiperalgesia, a main characteristic of neuropathic pain and therefore TNF alpha is postulated as a biomarker for painful changes after nerve injury. With the aim to characterize TNF alpha effects in chronic neuropathic pain and in diabetic neuropathy, a transgenic mouse model overexpressing TNF alpha cDNA under the peripheral myelin protein P0 promoter was generated. Here we characterized the overexpression of TNF alpha in myelinated Scs at different stages of myelination (postnatal days 5, 21 and 65) showing that high levels of TNF alpha in sciatic nerve leads to the downregulation of the major PNS myelin proteins (P0, MBP, PMP22, MAG) compared to wild type mice, correlating with the loss of structured myelin and an increase in p75NTR, a marker for immature and non-myelinated Scs in the sciatic nerve. Iba1 staining showed high levels of macrophage infiltration in both sciatic nerve and spinal cord tissues, compared with wild type animals. Stress conditions were induced by sciatic nerve crush surgery after which recovery and subsequent remyelination were delayed in the transgenic mice, as evaluated by the Sciatic Functional Index (SFI) and electrophysiological tests. On the other hand, mechanical and thermal nociception seemed to be unaltered, with or without lesion. This model could be helpful in the characterization of the role TNF alpha in pain development, injury and DPN as well as in developing efficient therapeutic strategies to modulate such pathological conditions.

CHARCOT-MARIE-TOOTH DISEASE: GENETIC SUBTYPES IN NORTHWESTERN SPAIN

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Charcot-Marie-Tooth (CMT) disease is a genetically heterogeneous group of hereditary motor and sensory neuropathies. More than 80 genes were involved in the disease pathogenesis. The objective of this study was to assess the genetic distribution of CMT disease in Galicia (Northwestern Spain). Patients were diagnosed as CMT if they had a consistent neurological and/or neurophysiological examination or if they had sensory motor neuropathy with a positive family history. A total of 215 CMT adult patients (55% females) were evaluated with a median age of 48 [39-60] years. The molecular diagnosis was achieved in 168 patients (78%) with a higher success in CMT1 (60%) than CMT2 (20%). Globally, *PMP22* duplication was the most frequent finding (55%), followed by mutations in *MPZ* (11%), *MFN2* (8%), *GJB1* (8%) and *GDAP1* (6%). In CMT1, with expception of the *PMP22* duplication, pathogenic variants in *EGR2*, *NEFL* and *MPZ* gene

were most common. Pathogenic variants in *MFN2* and *GDAP1* accounted for 70% of CMT2 patients. Several patients referred to our institution as CMT2 were diagnosed as hereditary motor neuropathy (HMN) and pathogenic variants in the *BSCL2* gene were the most frequent. Pathogenic variants not previously related to CMT were identified in *MPZ, MFN2, GJB1, EGR2, NEFL and SH3TC2* genes. Sporadic or autosomal recessive (AR) CMT accounted for the 30% of all diagnoses. The genetic epidemiology of CMT in Galicia follows a similar pattern to other populations, although some remarkable features are axonal *GDAP1* and demyalinating *EGR2* pathogenic variants as well a seemingly elevated proportion of AR cases.

A MPZ R98C CMT PATIENT PRESENTING A FLUCTUATING NEUROPATHY SUSCEPTIBLE TO TREATMENT

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Mutations in MPZ gene are associated to a wide range of phenotypes. The R98C, in particular, is associated to a severe and early onset disease. Some CMT patients respond to immunosuppressive or immunomodulatory treatment, some of them harbouring MPZ mutations. We present the case of a 34-year-old Brazilian female with a severe CMT1B (R98C) that presented an acute episode of worsening after a febrile exanthematic disease. She complained of tingling, stopped walking without support, and could not raise her arms. Her EMG showed an asymmetrical reduction of motor CV, reduced amplitudes, severe temporal dispersion and possibly conduction block. CSF protein was 130mg%, with normal cell count. Diagnosed as GBS, she received IVIg. Curiously, she markedly improved, regaining the functional status of youth, recovering functions that she had long lost. On EMG, motor amplitudes improved significantly, but CV remained the same. Reviewing carefully her past history, we identified some motor fluctuations along her adult life. At age 26, while pregnant, she developed positive sensory symptoms, became unable to get up from the chair and could not walk without assistance. After delivery, she improved, but did not return to baseline. One year later, she presented a new transitory functional worsening after an influenza illness. Her parents were healthy but two out her 3 children have a severe CMT. Her first daughter never walked and died at the age of six. Six months after treatment with IVIg, she faced a new relapse. We pulsed with corticosteroids, with great response. She remains stable to date, four months after treatment. The episodic fluctuations and the evident response to treatment clearly suggest an associated immunomediated process. The fast improvement of the amplitude with maintenance of CV suggests that another mechanism in addition to demyelination and axonal degeneration is involved. We propose the existence of an associated channelopathy.

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GBS CLASSIFICATION ACCORDING TO TWO-SETS OF EMG EXAMINATION IN A SAMPLE OF THE BRAZILIAN POPULATION

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GBS is an acute, immune-mediated neuropathy that comprises three major subtypes: AIDP, AMAN, and AMSAN. On clinical grounds, this distinction is based on nerve conduction studies (NCS): AIDP is a demyelinating neuropathy, AMAN is an axonal motor neuropathy, and AMSAN, an axonal sensory and motor neuropathy. Recently, it has been demonstrated that axonal GBS, in addition to axonal degeneration, may present conduction block (CB) that can progress to axonal regeneration or revert, characterising a *reversible conduction failure (RCF)*, a finding usually associated to good prognosis. Patients presenting axonal CB are frequently diagnosed as having AIDP, a mistake that can be avoided with two sets of NCS, one as early as possible and the second after three weeks of disease. Following these recommendations, we retrospectively classified a Brazilian group with GBS followed in our institution that had been submitted to two NCS sets. From September 2010 to January 2017, 52 patients fulfilled clinical criteria for GBS at Clinical Hospital of Ribeirão Preto and had more than one NCS accomplished. At least four motor nerves (median, ulnar, peroneal, and posterior tibial) and five sensory nerves (medial, ulnar, radial, sural, and peroneal superficial) were evaluated in each examination, according to routine procedures. First NCS revealed 12 patients with AIDP (23%), 29 cases of axonal GBS (21 AMAN, 8 AMSAN, 56%), and 11 patients with equivocal results (21%). At follow-up study, 15 patients (29%) had their classification changed. The main shifts were from AIDP to axonal group and from equivocal results to AIDP. AIDP increased to 31% (n = 16), axonal GBS increased to 69% (n = 36, 22 AMAN, 14 AMSAN), and there were no more equivocal patients. Although the majority of studies have shown that AIDP is more frequent in Western countries while axonal GBS predominates in Eastern countries, we found a different pattern of distribution in our population, with predominance of the axonal subtypes. The considerable increase of axonal GBS at follow-up studies reinforces that serial EMG are mandatory for accurate diagnosis of GBS subtypes. Prospective studies are now being carried out in order to confirm these results.

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NEOD001 DEMONSTRATES DURABLE PERIPHERAL NEUROPATHY RESPONSES IN PATIENTS WITH LIGHT CHAIN

AMYLOIDOSIS AND PERSISTENT ORGAN DYSFUNCTION: RESULTS FROM A PHASE 1/2 STUDY

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In amyloid light chain (AL) amyloidosis, misfolded light chain (LC) accumulates and causes progressive peripheral neuropathy (PN) and progressive failure of critical organs such as the heart and kidneys. Progressive ascending sensorimotor neuropathy is often a related clinical finding. The deposition of toxic LC amyloid in peripheral nerves is associated with paresthesias, pain, muscle weaknesss, orthostatic hypotension, and diarrhea or constipation in approximately 35% of patients with AL amyloidosis. There are no approved treatments for AL amyloidosis. Current therapeutic approaches for AL amyloidosis are intended to limit LC production but do not directly target misfolded LC deposited as amyloid in organs. We report phase 1/2 trial results of NEOD001, an investigational monoclonal antibody that targets misfolded LC and may neutralize circulating LC aggregates and clear insoluble deposits. Trial inclusion criteria were one or more plasma cell–directed treatment completed before enrollment, partial or greater hematologic response to any previous therapy, and persistent organ dysfunction. NEOD001 was administered intravenously every 28 days during a dose-escalation phase (27 patients; 0.5, 1, 2, 4, 8, 16, or 24 mg/kg in a 3+3 study design) and an expansion phase (42 patients; 24 mg/kg). We assessed safety, tolerability, pharmacokinetics, immunogenicity, organ responses based on consensus criteria, and PN responses using the Neuropathy Impairment Score–Lower Limb (NIS-LL). NEOD001 treatment was not associated with dose-limiting toxicities or serious adverse events, drug-related discontinuations, or antidrug antibody development in any patient (N = 69). Of patients with measurable PN at baseline (N = 11), 82% achieved PN response based on the NIS-LL score after 9 months of treatment, which resulted in a median 23% NIS-LL score reduction (mean baseline NIS-LL, 28.1). In a best response analysis, 53% of cardiac-evaluable patients (n = 36) and 64% of renal-evaluable patients (n = 36) met respective criteria for organ response. Improvements in neuropathy have not been previously shown in AL amyloidosis. These results demonstrated that monthly NEOD001 infusions were safe, well tolerated, and associated with responses across three different organ systems.

VENTRAL ABDOMINAL SENSORY LOSS IS COMMON IN LENGTH DEPENDENT SENSORIMOTOR PERIPHERAL NEUROPATHY

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This work describes clinical, examination and electrophysiologic findings in a cohort of patients with length dependent sensorimotor peripheral neuropathy (LDSMPN) with ventral abdominal sensory loss. LDSMPN affects the longest nerve fibers, namely those innervating structures in the feet and hands. What is less well appreciated is that length dependent involvement of sensory nerve fibers in LDSMPN from the thoracic segments gives rise to ventral abdominal sensory loss. Consecutive patients seen for LDSMPN (n= 77) were evaluated for the presence or absence of ventral abdominal sensory loss. Demographic variables, symptoms and quantitative neurologic findings (Neuropathy Impairment Score [NIS]) were examined using descriptive statistics. Final diagnoses were noted. Ventral abdominal sensory loss to pinprick (which was asymptomatic in all patients tested) was documented in 52/77 LDSMPN patients (67.5%), mean age was 61.7 years (range 33-89), M:F gender ratio was 1.7 (33:19), mean NIS was 19.1 (range 0-77), NCS/EMG abnormalities were found in 60/77 patients (the remaining 17 showing objective evidence of small fiber sensory involvement). LDSMPN patients without ventral abdominal sensory loss (n=25) had a mean age of 59.4 (range 31-77), M:F of 2.6 (18:7), and mean NIS of 21.8 (range 0-95). No patient (0/77) had dorsal torso sensory loss between the shoulder and buttock levels on either side. Diagnoses of the LDSMPN patients with vs. without ventral abdominal sensory loss included Charcot Marie Tooth or other hereditary neuropathy (n=3 vs.1), abnormal carbohydrate metabolism (n=17 vs. 3), idiopathic (n=12 vs.10), hypothyroidism (n=6 vs. 2), inflammatory (n=9 vs. 5) and other (n=5 vs. 4). Ventral abdominal sensory loss appears to be common in patients diagnosed with LDSMPN of a variety of causes including inherited neuropathies; in addition to those innervating distal limb territories, distal sensory fibers from the thoracic region represent another category of length dependent involvement in LDSMPN; 3) the clinical examination of LDSMPN should include the ventral abdomen.

STRUCTURAL AND FUNCTIONAL TESTS OF NEUROPATHY IN DIABETES

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OBJECTIVE: To determine the relationship between measures of autonomic function, electrochemical sweat conductance (ESC) and intra-epidermal (IENFD) and sudomotor nerve fiber density (SGNFD).

BACKGROUND: Structural and functional measures of small fiber neuropathy have been studied in patients with diabetes, but little information comparing these techniques exists.
DESIGN/METHODS: We studied 25 patients with diabetes (ages 57±11yrs, gender 9F) and 14 healthy control subjects (Age 54±13yrs, gender 7F). Subjects underwent examination scores (NIS-LL), quantitative sensory testing, autonomic testing (heart rate variability, Valsalva maneuver, tilt test), ESC, and 3 millimeter punch skin biopsies at the distal leg and distal thigh for IENFD & SGNFD.
RESULTS: There were strong correlations between exam scores (NIS-LL) and biopsy IENFD (R=-0.83, P<0.01 distal leg; R=-0.78, P<0.01 distal thigh), and SGNFD (R=-0.61, P<0.05 distal leg; R=-0.73, P<0.01 distal thigh). Moderate correlations were noted between exam scores and QST (R values 0.3-0.5, P<0.05), IENFD and QST (R=0.40-0.47). Modest correlations were noted between ESC and parasympathetic function (R=0.33-0.47, P<0.05). Modest correlations were noted between ESC and IENFD (R=0.34, P<0.05, but only at the distal leg) and ESC and NIS-LL (-0.33, P<0.05). No correlations between exam scores and autonomic function were noted. No correlations were detected between ESC and SGNFD (R=-0.09-0.32) or ESC and sympathetic adrenergic function (R=0.06).
CONCLUSIONS: Differences between tests are expected based on our understanding of the pathophysiology and natural history of diabetic neuropathy. Exam scores, QST results and biopsy results do correlate, and are consistent with prior studies. In contrast, there was little relationship between tests of autonomic function and exam scores, similar to prior studies and our understanding of autonomic function and differences in p. ESC had little correlation with either exam scores or biopsy IENFD or SGNFD. There was a modest correlation between ESC and parasympathetic function. The exact relationship between ESC and diabetic peripheral neuropathy is not clear, and further research studies are needed to determine the role this technique has in clinical practice.

IMPLICATIONS OF SKIN BIOPSY TISSUE THICKNESS ON STUDY OUTCOMES

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OBJECTIVE: To determine the optimal tissue thickness of skin biopsy sections for studies of cutaneous nerve fibers.
BACKGROUND: Although analysis of intra-epidermal nerve fiber density (IENFD) is routinely reported using 50 µm thick tissue sections, many recent studies of peripheral alpha-synuclein deposition use 20 or 10 µm frozen sections, or 5 µm paraffin embedded tissue sections.
DESIGN/METHODS: We compared the results of biopsies from 30 patients with Parkinson's disease (PD), using 4 tissue sections each of 50, 20 and 10 µm thickness. Tissues were stained with PGP9.5 and stained for phosphorylated alpha-synuclein (P-SYN). The total number of dermal structures (hair follicles, sweat glands, pilomotor muscles) were quantified, nerve densities analyzed, and the frequency of P-SYN positive results. We also studied 5 µm paraffin embedded tissue samples from 11 patients with PD.
RESULTS: In the 30 biopsies of patients with PD there were no differences in the number of sweat glands, hair follicles or pilomotor muscles in 50, 20 or 10 µm sections. There were significantly fewer blood vessels noted in 20 and 10 µm sections compared to 50 µm sections (P<0.05). IENFD and SGNFD declined with tissue thickness (P.0.01, all) and there was increased variability in results in thinner tissue sections. There was a highly significant reduction in P-SYN positive sections in thinner tissue sections (P<0.001, all tissues compared to 50 µm sections). Paraffin embedded tissue sections had significantly lower nerve densities and positive P-SYN results (P<0.01) compared to all frozen tissue sections of 50, 20 and 10 µm thickness. Thinner tissue sections carried a greater risk of false positive result or indeterminate results due to difficulty interpreting overlap with PGP9.5.
CONCLUSIONS: Tissue sample thickness plays a critical role in interpretation of skin biopsy results. Thinner tissue sections, or paraffin embedded tissue sections, do not provide equivalent data and significantly underestimate nerve densities and positive alpha-synuclein results with increase false positive results despite similar numbers of dermal tissue structures.

AN ONGOING PHASE 2 STUDY EVALUATING THE SAFETY, EFFICACY, AND PHARMACOKINETICS OF ACE-083 IN PATIENTS WITH CMT1 AND CMTX.

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ACE-083 is an investigational protein therapeutic that acts as a localized ligand trap for myostatin and other negative regulators of muscle growth. Local injection of ACE-083 into the gastrocnemius muscle of wild-type, *mdx*, and SOD1 mice produced dose-dependent increases in muscle mass and force without systemic effects. In a Phase 1 single-center, double-blind, placebo-controlled dose escalation study in post-menopausal women, unilateral injections of ACE-083 into the rectus femoris (RF) or tibialis anterior (TA) muscle were generally safe and well tolerated. Mean percent changes from baseline in muscle volume of the injected muscle were +14.5% in the RF and +8.9% in the TA at the highest dose administered with minimal changes observed in the contralateral side and placebo-treated subjects. Frequent related AEs (≥15%) included injection site pain, pain in extremity, injection site discomfort, and muscle twitching, with similar incidence in ACE-083 and placebo-treated groups. All AEs were grade 1-2 and reversible. Together, these preclinical and clinical results support further studies of ACE-083 in myogenic and/or neurogenic diseases with focal loss

of muscle strength and function, including CMT. A Phase 2 study is ongoing in facioscapulohumeral muscular dystrophy (FSHD). Study A083-03 is an ongoing multicenter, two-part, Phase 2 study to evaluate the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of ACE-083 in patients with CMT1 and CMTX. Part 1 is open-label and will enroll up to 3 dose-escalating cohorts (6 patients per cohort); Part 2 is randomized, double-blind, and placebo-controlled, and will enroll an additional 24 patients. ACE-083 will be administered bilaterally to the TA muscle once every three weeks for up to five doses. A Safety Review Team will meet periodically throughout the study to review safety data and make dosing recommendations, including the recommended dose level for Part 2. Eligible patients must have genetically confirmed CMT1 or CMTX with mild-moderate weakness in ankle dorsiflexion. Safety and tolerability will serve as the primary outcome for Part 1, muscle volume evaluated by MRI for Part 2. Additional outcome measures of interest include strength by quantitative muscle testing, function by motor tests, and quality of life by the CMT-Health Index questionnaire.

FUNCTIONAL AND MORPHOLOGICAL CONSEQUENCES OF CELLULAR AND HUMORAL RESPONSES IN TREATMENT-NAIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A COMBINED SONOGRAPHIC AND NERVE CONDUCTION STUDY.

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Keywords: CIDP – MMN – MRI – Ultrasound – Nerve hypertrophy

Our study was aimed to evaluate the functional and morphological consequences of cellular and humoral responses in chronic inflammatory demyelinating neuropathy (CIDP), using extensive standardized high-resolution sonography (HRUS) and nerve conduction study (NCS) protocols in incident treatment-naive patients.
We enrolled 50 consecutive, newly diagnosed, treatment naive patients with CIDP. In addition to all relevant clinical examinations, all patients underwent a standardized NCS and extensive HRUS protocol, of median, ulnar, tibial, fibular and sural nerves. We assessed standard nerve and fascicle size, and echogenicity.
We found focal sonographic enlargements in multiple nerves and nerve segments with and without NCS abnormalities. The degree of nerve hypertrophy was not associated with presence of NCS features of demyelination, i.e. 84/132 (64%) of median nerve segments showed enlargement without strong decrease in motor conduction velocity and 102/111 (92%) hypertrophic median nerve segments revealed no conduction block. A lower distal CMAP of median nerve was related with lower MRC sums-scores ($p < 0.001$). We found no correlation between age, disease duration or MRC sum-score and nerve size. Cellular and humoral responses in CIDP may lead to nerve enlargement along the length of nerves, that can be detected by HRUS, whereas NCS allows identification of its' specific focal disruption in nerve function.

SCHWANN CELL p75NTR EXPRESSION AND DIABETIC NEUROPATHY

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The most common complication of diabetes is peripheral neuropathy, which has prevalence as high as 50% and is characterized by damage to neurons, Schwann cells and blood vessels within the nerve. The concept of Schwannopathy as an integral factor in the pathogenesis of diabetic neuropathy is re-emerging, and it is now known that Schwann cells cultured in hyperglycemic environments underproduce neurotrophins and exhibit loss of axonal associations, further indicating a non-optimal glial cell activation and function. Furthermore, the increased expression of $p75^{NTR}$ in myelin sheaths around fibers that are susceptible to axonal degeneration in diabetic neuropathy suggest an important role for this molecule in disease progression. With this project, it is our main goal to evaluate how disruption of $p75^{NTR}$ signaling in the Schwann cells affects the pathophysiology of diabetic neuropathy.
By using a fluorescent live/death cell viability assay, our preliminary data indicate that wild-type Schwann cell cultures present increased cell death rate 24h after stimulation with high levels of glucose. The $p75^{NTR}$ has a highly recognized role in the activation of death signals and when absent, we observed that Schwann cells are significantly more resistant to apoptosis in hyperglycemic conditions. The role of $p75^{NTR}$ receptor signaling in neuron-Schwann cell communication and myelination under *in vitro* diabetic conditions was investigated with primary Schwann cell-sensory neuron co-cultures. After eight days of ascorbic acid stimulation, both under euglycemic and hyperglycemic conditions, myelination was assessed by confocal microscopy using specific markers for neurons and myelin. Results highlight a compromised

ability of wild-type Schwann cells to myelinate axons when exposed to a hyperglycemic environment, which was even intensified in co-cultures with Schwann cells lacking the $p75^{NTR}$. To complement the *in vitro* studies, we are modeling type 2 diabetes in a $p75^{NTR}$ Schwann cell conditional KO mouse model and plan to investigate nerve mRNA expression profile to disclose genetic regulation depending on this receptor signaling and its modulatory role in endoneurial hypoxia and neuroinflammation.
The results from this project will provide an integrated vision of how impaired Schwann cell activity guides neuropathy progression.

DEFINITION AND DIAGNOSIS OF SMALL FIBER NEUROPATHY (SFN): RECOMMENDATIONS FROM THE BRAZILIAN ACADEMY OF NEUROLOGY

Gondim FAA; Barreira AA, Cruz MW, Cunha FMB, De Freitas M, França Jr MC, Marques Jr W, Nascimento OJM, Oliveira ASB, Pereira RC, Pupe C, Rotta FT, Schestatsky P. Panelists on behalf of the Scientific Department of Peripheral Neuropathy, Brazilian Academy of Neurology, Brazil.

Neuropathy is one of the most common neurological manifestations of several diseases and SFN has been progressively receiving more attention in the medical literature. The aim of this study is to generate a set of recommendations to define and diagnose SFN in Brazil. A group of 13 neurologists, members of the Scientific Department of Peripheral Neuropathy from the Brazilian Academy of Neurology reviewed a preliminary draft prepared by the first author that was distributed by email. The panelists got together on 6.4.2017 at the city of Fortaleza, Brazil, to discuss and finish the text for the first submission of the manuscript. SFN can be defined as a subtype of neuropathy characterized by selective involvement of unmyelinated or thinly myelinated sensory (sometimes also autonomic) fibers. It is usually characterized by sensory (pain/dysesthesias/pruritus) or combined sensory and autonomic complaints, associated with an almost entirely normal neurological examination (except for sensory changes). Electromyography is normal. A growing list of medical conditions has been linked to SFN, although there is no evidence-based literature to support the use of any specific set of screening tests to diagnose the etiology of SFN (the panelists will suggest a basic screening panel). SFN may also serve as a fallacious but useful terminology to uncover discrepancies in the normal values from different neurophysiology laboratories. In Brazil, skin biopsy is not usually performed and initial forms of leprosy may have predominant small fiber involvement. There are several tests to demonstrate involvement of small sensory and autonomic fibers. Skin wrinkling test, sympathetic skin responses & heart rate variability (conducted on EMG machines) and thermoregulatory sweat test may be low-cost screening alternatives. After the final meeting on 6.4.2017, we finished the first draft for submission to Arquivos de Neuropsiquiatria (together with a translation to Portuguese as supplementary material), the official journal of the Brazilian Academy of Neurology to serve as a source for the definition and diagnosis of SFN in Brazil. The final draft will be submitted after presentation at the PNS Meeting in Barcelona on 7.2017.

IMAGING OF THE LOWER CRANIAL NERVES (LCN) IN THE EXTRACRANIAL COURSE

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The lower cranial nerves (LCN) include the paired glossopharyngeal, the vagal, the accessory and the hypoglossal nerves. These are involved in the execution of swallowing, speech, phonation, tasting, as well as sensory and autonomic functions. LCN can be affected in central and peripheral nervous system diseases.
This study investigates the use of ultrasound (US) to detect lesions of the peripheral course of LCN. In addition MRI can be used in unilateral LCN local lesions to demonstrate indirect signs of nerve lesions such as muscle atrophy.
The patients were examined in supine position with the neck in maximum extension with either a regular or a portable US system (LOGIQ e and Logiq E9 GE Healthcare, Milwaukee, Wisconsin) and high frequency transducers (12 to 20 Mhz). According to the detected pathology longitudinal or transversal images were recorded.
A series of exemplary observations are demonstrated.
In one case a paraganglioma in the glossopharyngeal nerve at the carotid sinus was found. In another patient an US of the thyroid gland revealed a nerve tumor, which was later identified to be a schwannoma. In another case multiple neurofibroma were identified in the vagal nerve during a routine neurofibromatosis screening.
US has become also important in investigations of lesions of the accessory nerve, following damage by surgery. Nerve continuity and scar formation can be distinguished. Lesions of the hypoglossal nerve can be caused by tumor infiltration. In one patient an infiltration of the nerve by a squamous cell carcinoma, and in another case by a low grade sarcoma were detected. In addition MRI demonstrated an atrophy of the tongue.
Identification and assessment of the LCN from the point of exit of the skull to their endpoint can be pursued by US techniques, which have been described for the individual nerves. US is easily applicable and – in addition to the „static“ image of the MRI – allows assessing nerve positions during different movements, as well as detecting muscle movements as fasciculations.

MRI can also be used to detect not only more proximal lesions, but also changes of the skeletal muscle by denervation.

AUTOIMMUNE T CELLS IN AN EX VIVO MODEL OF THE PERIPHERAL NERVOUS SYSTEM

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In chronic inflammatory demyelinating polyneuropathy (CIDP), T cells are suspected to play a crucial role in myelin destruction. CD4 and CD8 T cells contribute to the inflammatory process, while the exact mechanism of myelin damage is still under debate. To elucidate the molecular interaction of T cells and myelin sheets, we compared neuritogenic and control cells in a live imaging *in vitro* model.
The myelinated fibres of rat dorsal root ganglia (DRG) served as model for the peripheral nervous system. DRGs of embryonic (E16) Lewis rats were cultured; myelination was initiated after one week *in vitro* and continued for two additional weeks.
Lewis rats immunized with P2 and neuritogenic T cells of the lymph nodes were obtained ten days after immunization. Control T cells were prepared from healthy rats. For vital tracking, neuritogenic T cells were stained with Orange Cell Tracker, while the control cells were labelled with CFSE. Myelin detection in vital cultures was assessed by incorporation of C16 fatty acids conjugated with a fluorophore into the myelin layer. Experiments were performed in a conditioned microscope chamber, the two T cell populations were added simultaneously to the DRG culture and migration was tracked using live cell imaging.
We observed differing migration patterns for neuritogenic and control T cells. The velocity as well as the directionality was altered. After initial contact, the non- neuriotgenic T cells in close proximity to myelin subsequently decreased over time, while the numbers of neuritogenic T cells close to myelin remained stable. Long term incubation with neuritogenic T cells affected the myelin integrity in regard to the intermodal length as well as the myelin ratio. Further experiments will elucidate the specific effects of neuritogenic T cells to decipher the role of T cells during inflammation in the PNS, which could be useful in developing targeted therapies.

TAFAMIDIS DELAYS DISEASE PROGRESSION COMPARABLY ACROSS VAL30MET AND NON-VAL30MET GENOTYPES IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, life-threatening disorder caused by protein destabilizing *TTR* gene mutations, broadly classified as Val30Met (the most common mutation worldwide) and non-Val30Met genotypes. Tafamidis, a highly-specific TTR-stabilizer, is the only medicine approved to delay neurologic progression in TTR-FAP. The objective of this post-hoc analysis was to compare the effects of tafamidis on neuropathy progression in patients with Val30Met and non-Val30Met genotypes. Val30Met patients were participants in a randomized, double-blind, placebo-controlled clinical trial of tafamidis, while non-Val30Met patients were participants in an open-label tafamidis study. Patients were grouped into three cohorts: Val30Met tafamidis (n=64); Val30Met placebo (n=61); and non-Val30Met tafamidis (n=21). Baseline disease severity and change in disease severity from baseline to month 12 was assessed using the Neuropathy Impairment Score-Lower Limbs (NIS-LL). The effect of tafamidis in the Val30Met and non-Val30Met cohorts versus the Val30Met placebo cohort was determined using a mixed-effects model for repeated measures (MMRM). At baseline, patients in the non-Val30Met cohort were older, had longer symptom duration, and more advanced neurologic impairment than the Val30Met cohorts. At month 12, the baseline-adjusted mean ± standard error change in NIS-LL was comparable between the Val30Met tafamidis and non-Val30Met tafamidis cohorts (1.60±0.78 and 1.62±1.43, respectively). These changes were smaller than that observed in the Val30Met placebo cohort (4.72±0.77; P=0.0055 vs Val30Met and P=0.0592 vs non-Val30Met) indicating less disease progression. Based on predicted values from the MMRM analysis, the size of the change in NIS-LL across the full range of baseline NIS-LL scores was remarkably similar in the Val30Met tafamidis and non-Val30Met tafamidis cohorts and was consistently smaller than that observed in the Val30Met placebo cohort. Moreover, in all three cohorts, as baseline NIS-LL increased, the predicted level of disease progression also increased. In conclusion, while controlling for baseline disease severity, tafamidis delayed disease progression to a comparable extent in Val30Met and non-Val30Met patients. The similar trajectories of disease progression across Val30Met and non-Val30Met patients suggest that these two genotype groups may be more similar than previously considered. ClinicalTrials.gov identifiers: NCT00409175; NCT00630864.

PROLONGED POST TETANIC POTENTIATION

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Post tetanic potentiation (PTP) is a physiological phenonmenon seen with disorders of the neuromuscular junction (NMJ). It is caused by the influx of Ca++ into the terminal axon during the tetanus resulting in an increased number of acetylcholine (Ach) vescicles released by each axonal action potential. In myasthenic syndromes it results in improved NMJ function by increasing the

probability of achieving a large enough end plate potential to generate a muscle action potential. PTP has different appearances depending on whether the NMJ defect is pre-synaptic or post-synaptic. In pre-synaptic defects (the most common being Lambert-Eaton syndrome) there is an increased amplitude of the muscle action potential after a tetanus that persists up to minutes. Prolonged PTP has now been reported in 2 disorders, one on a genetically determined neuropathy/myasthenic basis and the other on an acquired toxic origin.
Prolonged PTP up to 60 minutes was reported in 2 families with a motor neuropathy (having leg weakness and foot deformites) and a congenital myasthenic syndrome caused by a heterozygous mutation of the synaptotamin II (SYT2) gene (c920T>G p.Pro308[p.Asp307Ala] and c923G>A [p.Pro308Leu]). Electrophysiological testing showed features of a presynaptic defect with prolonged PTP persisting up to 60 minutes. The same phenomenon has been noted in the acquired pre-synaptic defect caused by botululinum toxin. The PTP continued up to 21 minutes. SYT2 is the synaptic vescicle calcium sensor in the terminal axon, allowing for fusion of Ach containing vescicles with the presynaptic membrane and the synchronous release of Ach. The fusion requires a complex assembly process involving SNARE proteins. Both the SYT2 gene mutation and botulinum toxin affect normal SYT2 function, the mutation by altering amino acids in the calcium-binding domain and the toxin by binding to SYT2 as well as gangliosides GD1a and GT1b on the neural membrane. The mechanism for the PTP prolongation remains unknown. Prolonged PTP appears to be a unique physiological abnormality resulting from altered SYT2. This phenomenon has been decribed to occur in SYT2 mutations causing congenital motor neuropathy/myasthenic syndrome and botulism. The abnormality may represent a physiological marker for a presynaptic NMJ defect involving altered SYT2.

THE MODIFIED MULTIPLE POINT STIMULATION METHOD FOR MOTOR NUMBER UNIT ESTIMATION

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Background: Motor unit number estimation (MUNE) techniques are valuable tools in neuromuscular disease. Among them, the multiple point stimulation (MPS) is one of the most common used. Contamination by distant single motor unit potentials (SMUPs) generated by neighboring muscles is a potential confounding factor. This is particularly problematic in ulnar neuropathy, one of the most common neuropathies in humans. Reason being that the ulnar nerve innervates the majority of hand muscles. The goals of this study are to test the hypotheses that 1) distant SMUPs all have an initial positive deflection and 2) elimination of SMUPs generated by distal muscles will significantly lower the MUNE results in the hypothenar muscles.
Methods: To address the first hypothesis, we tested 10 subjects by stimulating their median nerve while recording SMUPS simultaneously over the hypothenar and thenar muscles. For the second hypothesis, we carried out MPS MUNE of the hypothenar muscles using multi-channel recordings placed over ulnar innervated intrinsic muscles across the hand. When a SMUP with an initial positive deflection was detected at the hypothenar electrodes, its original was systemically tracked through all the recording channels.
Results: In the first series of experiments, in accordance with the dipole theory, all SMUPs recorded at the hypothenar recording electrodes had an initial positive polarity. In the second series of experiments, of the 41 studies carried out in 28 subjects, distant SMUPs generated by muscles other than those in the hypothenar eminence represented 17±9.5% (mean±SD) of the overall sample. MUNE calculated using only SMUPs generated by the hypothenar muscles was 423± 204, compared to 537±290 if all SMUPs were included ($p < 0.05$). The extent of increase in MUNE was highly correlated with the proportion of distant SMUPs found in each study ($r = 0.89$, $p < 0.05$).
Conclusion: In contrary to some studies suggesting that SMUPs from distant muscles could have an initial negative deflection, we found all SMUPs from distant muscles had a positive deflection. Exclusion of those SMUPs from the sample had a significant impact on the MUNE results.

CILOSTAZOL MODULATES SEQUENTIAL EXPRESSION OF MATRIX METALLOPROTEINASES AND THEIR INTRINSIC INHIBITOR WITHIN PERIPHERAL NERVOUS TISSUE DURING EXPERIMENTAL AUTOIMMUNE NEURITIS

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Matrix metalloproteinase (MMP) plays crucial roles in developing immune-mediated neuritis as Guillain-Barré syndrome (GBS) and its animal model experimental autoimmune neuritis (EAN). To investigate the intraneural expression of MMPs during EAN and the effect of a phosphodiesterase-3 inhibitor cilostazol (CLZ) on it, EAN rats were treated with either 30 mg/kg/day of CLZ or vehicle from one day post immunization (dpi). To induce EAN female Lewis rats were immunized with synthetic peptide from bovine P2 protein. Cauda equina (CE) were removed in several time points, total RNA was extracted and reverse-transcribed to obtain cDNA that was subjected to Real-time PCR analysis for expression of MMP-7, MMP-9 and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) messages. MMP-7 and MMP-9 messages peaked at 7 dpi, that is presymptomatic phase of EAN. All rats developed motor paralysis at 11 dpi, MMP-7 and MMP-9 messages subsided at this moment. However, TIMP-1 message reciprocally increased at 11 dpi, persisted through 21 dpi. Treatment of CLZ suppressed motor

paralysis of EAN significantly. MMP-7 message peaked at 14 dpi and MMP-9 message peaked at 11 dpi. On the other hand, both messages at 7 dpi were suppressed compared to untreated EAN rats. TIMP-1 message in CLZ treated rats peaked at 14 dpi coincided with motor paralysis peak. Both MMP-7 and MMP-9 messages might result in subsequent upregulation of TIMP-1 that finally downregulates MMPs activity and inflammatory process. CLZ treatment suppressed and delayed expression of MMPs and facilitate TIMP-1 expression, resulting suppression of EAN. The precise mechanism of expression of MMPs and TIMP-1 remain unclear, however, that MMP-7 and MMP-9 messages peaked at 7 dpi suggests involvement of pro-inflammatory cytokines such as tumor necrosis factor-alpha or interleukin-1. CLZ might suppress these cytokines resulted in MMPs down regulation. MMP-9 less affected by CLZ and thus stimulated TIMP-1 expression at 14 dpi. CLZ might rational treatment for immune-mediated neuropathy via MMPs modulation although further investigation especially in-vivo study is needed.

IMPAIRMENT OF AUTOPHAGY AS A POSSIBLE PATHOMECHANISM FOR CMT CAUSING MUTATIONS IN HSPB1

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The small heat shock protein *HSPB1* (*HSP27*) gene is ubiquitously expressed and encodes for a chaperone protein with essential cellular functions. Our lab was the first to identify missense mutations in *HSPB1* responsible for axonal Charcot-Marie-Tooth neuropathy (CMT2F). Since then we became interested in understanding the physiological functions of HSPB1 and its association with CMT neuropathies. We demonstrated the involvement of HSPB1 in microtubule stability. Because of the link between autophagosome formation and its intracellular transport, and microtubules stability, we believed that the macro-autophagy process could be regulated by HSPB1. Macro-autophagy is a cellular housekeeping process during which autophagosomes target, envelop and degrade aberrant protein aggregates and damaged organelles. There is strong evidence for an essential role for autophagy in the maintenance of neuronal homeostasis; hence its impairment can lead to a neuropathic condition. Our data indicate that macro-autophagy is disrupted by HSPB1 CMT-causing mutations. Combining novel microscopy and interactomics techniques we unravelled the way different CMT-causing mutations in *HSPB1* impair the autophagic pathway. Our data present the impairment of autophagy as a possible pathomechanism for CMT-causing HSPB1 mutations.

GENE THERAPY ON RATS MODELS OF THE PERIPHERAL NEUROPATHY CHARCOT-MARIE-TOOTH

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CMT1A, the most common of Charcot-Marie-Tooth diseases, results from the duplication of Peripheral Myelin Protein 22 (PMP22) gene. This gene encodes for a small protein of 22 kDa, PMP22, mainly produced by Schwann cells and the excess of PMP22 leads to demyelination. There is no cure for this disease but one approach for a treatment is gene therapy. A transgenic rat model exists for CMT1A, which possesses 3 copies of the mouse PMP22 gene. Our goal is to provide a proof of principle for gene therapy in peripheral nerves using this rat model of CMT1A. Our strategy is to reduce the overexpression of mouse PMP22 protein in rats Schwann cells using short hairpin RNAs (shRNAs). shRNAs are small non-coding RNAs that specifically bind to targeted mRNAs resulting in their degradation. We tested for the efficiency of several shRNAs targeting mouse PMP22 *in vitro* to find two shRNAs that reduce PMP22 levels. The shRNAs have been cloned in an adeno-associated serotype 9 (AAV9) viral vector together with Green Fluorescent Protein in order to detect infected cells. AAV9 was selected for its high transduction rate of myelinating Schwann cells, for its good diffusion and low immunogenicity. We plan bilateral injections in the sciatic nerve of control and diseased rats. The efficiency of this gene therapy will be checked by assessing muscle strength (grip test), way of walking (catwalk), mobility (rotarod) and nerve conduction velocity of treated CMT1A rats versus non-treated. The process of myelination and myelin maintenance in Schwann cells will be analyzed by biochemistry and electron microscopy. Biochemical tests include Western Blot for PMP22 protein expression in sciatic nerve, immunohistochemistry for PMP22 protein expression in myelinating Schwann cells and PCR for mRNA PMP22 expression. If the therapy is successful in rats, it could possibly be later on used in clinical trials.

MEDIAN NERVE ULTRASOUND MORPHOLOGY CADAVER SCREENING

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Ultrasound is a widely-used tool in diagnosing carpal tunnel syndrome (CTS). Several different methods for sonographical evaluation of median nerve damage exist, such as calculating the ratio of cross sectional areas (CSA) of median nerves in various sites. This enables detection of actual nerve swelling

proximal to the carpal tunnel as an expression of median nerve damage inside the carpal tunnel (as seen in CTS). In comparison to other diagnostic methods no data exist about the prevalence of CTS like changes in an unselected population.
A series of 166 non-selected fresh cadavers were examined. 332 arms of 166 fresh, non-embalmed whole body cadavers were examined. The medical record did not allow to obtain conclusive information on the peripheral nerves. Using a regular ultrasound system with a 14 Mhz transducer, median nerves were identified and tracked along their course in the forearms. CSA measurements of the median nerves were performed at two sites in each arm: 1.) halfway between the elbow joint and wrist, 2.) directly proximal to the carpal tunnel. CSA ratio was calculated with the following formula: $CSA\ ratio = \frac{CSA^{\text{wrist}}(cm^2)}{CSA^{forearm}(cm^2)}$
CSA ratio < 1.5 was found in 282 (84.93%) arms, CSA ratio ≥ 1.5 in 40 (12.04%) arms and CSA ratio ≥ 2 in 10 (3%) arms. CSA ratio ≥ 1.5 was detected in 17.58% of women and 12% of men. The overall mean (± SD) age was 80.52 ± 10.04 years. Men (78.56 ± 10.16) were significantly younger than women (82.14 ± 9.6; p=0.001). A weak but significant correlation between age and CSA ratio was found in women (Spearman-□□ -0.185; p=0.013), but not in men (p=0.79). The mean BMI for CSA ratio ≥ 1.5 was 26.54 ± SD 5.35.
Based on a CSA ratio ≥ 1.5 as a criterion for CTS, the present ultrasound results are consistent with the average CTS prevalence reported in previous studies, which were obtained with electrophysiological methods. This study on a large unselected series of cadavers confirms the comparability of both methods.

POLYNEUROPATHY RELATES TO IMPAIRMENT IN DAILY ACTIVITIES, WORSE GAIT AND FALL-RELATED INJURIES

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Polyneuropathy is a common and disabling disorder, but population-based data about important patient-orientated outcomes, such as the ability to perform activities of daily living, risk of falls and related injuries, and gait patterns is scarce. Therefore we extensively investigated the association of chronic polyneuropathy with basic and instrumental activities of daily living (BADL and IADL), falls and gait patterns in the large, prospective, population based Rotterdam Study. In total, 1445 participants of this study (mean age 71 years, 54% women) underwent a polyneuropathy screening involving a symptom questionnaire, neurological examination and nerve conduction studies. Screening yielded four groups: no, possible, probable and definite polyneuropathy. Participants were interviewed about BADL (Stanford Health Assessment questionnaire), IADL (Instrumental Activities of Daily Living scale) and frequency of falling in the previous year. In a random subset of 977 participants, gait was assessed with an electronic walkway (GAITRite). Associations of polyneuropathy with BADL and IADL were analyzed continuously with linear regression, and dichotomously with logistic regression. History of falling was evaluated with logistic regression and gait changes were evaluated with linear regression. We found that participants with definite polyneuropathy had more difficulty in performing BADL and IADL than participants without polyneuropathy. Polyneuropathy related to worse scores of all BADL (especially walking) and three IADL components (housekeeping, traveling, and shopping). Participants with definite polyneuropathy were two times more likely to fall, and these falls more often resulted in injury. Participants with polyneuropathy had worse gait parameters on the walkway, including lower walking speed and cadence, and more errors in tandem walking. In summary, chronic polyneuropathy is strongly associated with significant impairment in daily life. Recognition of polyneuropathy and related disability is very important in order to inform, support and possibly treat patients, and to prevent future falls and dependence in daily functioning.

DIAGNOSTIC VALUE OF SYMPTOMS IN CHRONIC POLYNEUROPATHY: THE ERASMUS POLYNEUROPATHY SYMPTOM SCORE (E-PSS)

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Patients with polyneuropathy often suffer from tingling sensations, numbness, weakness and pain. These symptoms are used in several screening questionnaires, most of which were developed for high-risk patient groups, such as individuals with diabetes mellitus. In most tools equal weights are applied to all symptoms, while some might be more informative than others. We evaluated the diagnostic value and frequency of occurrence of individual symptoms of chronic polyneuropathy and constructed and validated a simple screening questionnaire that can reliably help to diagnose polyneuropathy in low-risk patient groups. In a multi-step procedure, we initially compiled a twelve-item questionnaire concerning symptoms of polyneuropathy. The questionnaire was completed by 117 polyneuropathy patients and 188 controls (headache, transient ischemic attack, multiple

sclerosis). We calculated the sensitivity, specificity and likelihood ratios of each individual symptom. Next, stepwise multivariable logistic regression was used to create a compact model, able to discriminate cases from controls using only the most informative symptoms. A simple scoring system was subsequently developed based on the regression coefficients of this reduced model. External validation was subsequently conducted in a population of 140 cases with chronic idiopathic axonal polyneuropathy and 96 controls without polyneuropathy. Performance was assessed with discrimination (area under the curve, AUC), and calibration. Numbness and tingling feet were most frequently reported by polyneuropathy patients and had the highest sensitivity. Feeling as if walking on cotton wool and allodynia of the feet had the highest specificity. Multivariable logistic regression yielded a model that contained these four symptoms, complemented with balance problems and tingling hands. Based on this regression analysis, the Erasmus Polyneuropathy Symptom Score (E-PSS) was created, a score ranging from 0 to 14. This polyneuropathy symptom score had a good performance (AUC 0.92) in de derivation set and proved to be valid in the external population (AUC 0.95). In this study, we created a simple, validated polyneuropathy symptom score (E-PSS) that takes both the individual value of only six different symptoms and its frequency into account. This tool can be helpful as screening instrument in clinical practice and for future studies on polyneuropathy.

MR-NEUROGRAPHY DETECTS INVOLVEMENT OF THE PERIPHERAL NERVOUS SYSTEM IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is traditionally viewed as a central nervous system disease. To date, there is no unequivocal evidence implicating involvement of the peripheral nervous system (PNS). This study aims to prove whether the PNS is additionally affected and if so, to detect, localize and quantify these peripheral nerve lesions in patients with multiple sclerosis (MS) by applying high-resolution MR-Neurography (MRN) with large anatomical coverage in combination with standard electrophysiological and neurological tests. We prospectively enrolled 34 patients with confirmed MS (>3 years), two patients with clinically isolated syndrome (CIS), and 35 age-/sex-matched healthy volunteers. Any other potential causes for a concomitant polyneuropathy were excluded. All MS patients underwent detailed neurological and electrophysiological testing. 3 Tesla MRN with large anatomical coverage from lumbar plexus and spinal nerves down to ankle level was performed in all participants by using fat-saturated, T2-weighted turbo-spin-echo (TSE) sequences (TR/TE 5970/55 ms) and a dual echo TSE sequence for T2-relaxometry (TR 5210 ms; TE_1/TE_2 12/73 ms). A 3D T2-weighted, fat-saturated SPACE sequence (TR 3000 ms; effective TE 210 ms) was used for imaging of the lumbar plexus. Manual segmentation of spinal/sciatic/tibial/peroneal nerves was performed on a total of 15,975 axial slices. Besides evaluation of nerve T2w-signal, detailed quantification of nerve lesions by analyzing morphometric (nerve caliber) and microstructural markers (proton-spin-density and T2-relaxation-time) was conducted.
Mean lesion load at thigh level was higher in MS (151.5±5.7) vs. controls (19.1±2.4;$p<0.0001$). Nerve proton-spin-density was also higher in MS (tibial/peroneal: 371.8±7.7 / 368.9±8.2) vs. controls (tibial/peroneal: 266.0±11.0 / 276.8±9.7;$p<0.0001$). In contrast, T2-relaxation time was significantly higher in controls (tibial/peroneal: 82.0±2.1 / 78.3±1.7) vs. MS (tibial/peroneal: 64.3±1.0 / 61.2±0.9;$p<0.0001$). Proximal tibial and fibular nerve caliber was also significantly higher in MS (tibial: $p<0.0015$; fibular: $p=0.0049$).
For the first time, PNS lesions in MS patients could be visualized and quantified in vivo by high-resolution MRN. Lesions are indicated by an increase of proton-spin-density and a decrease of T2-relaxation-time. Nerve caliber as a morphometric criterion also significantly increased. This proof-of-concept study may offer new insights into the pathomechanism of MS and might have future implications on therapeutic approaches.

THE ROLE OF IMMUNOGLOBULIN G FC-GAMMA RECEPTOR POLYMORPHISMS IN THE PATHOGENESIS OF GUILLAIN-BARRÉ SYNDROME IN BANGLADESH

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Immunoglobulin G (IgG) Fc-gammaRs confer diverse effector functions by linking the cellular and humoral arms of the immune system that has been involved in the pathogenesis of Guillain-Barré syndrome (GBS). In the post-polio era, the polymorphisms of Fc-gammaR and their relevant knowledge have become one of the main targets for new therapeutic strategies for the treatment of GBS patients. Differences in severity and frequency of GBS subtypes found between South-Asian and Western populations can be attributed to their genetic susceptibility. Therefore, we aimed to determine Fc-

gammaR polymorphic alleles (Fc-gammaRIIa: H131/R131; Fc-gammaRIIIa: V158/F158; Fc-gammaRIIIb: NA1/NA2) and their possible link with GBS on the currently available large GBS cohort in Bangladesh. Fc-gamma R polymorphisms of 151 GBS patients and 151 healthy controls were genotyped using sequence-specific PCR. For validation, we carried out the sequencing of some samples for Fc-gammaRIIa and Fc-gammaRIIIa alleles. No significant differences were found regarding the distribution of Fc-gammaR genotypes and allele frequencies in GBS patients and controls. Fc-gammaR-H/H-131 genotype was significantly predominant in patients with severe disease compared to patients with mild disease (p=0.02, OR, 2.8; 95% CI, 1.2-6.6). No other significant associations were found in GBS patients for candidate alleles and disease severity. Fc-gammaRIIIa-F/F-158 was found to be significantly predominant in anti-GM1 antibody positive GBS patients compared to anti-GM1 antibody negative patients (p=0.02, OR, 2.5, 95% CI, 1.2-5.3). Fc-gammaRIIIa-V158 alleles were significantly higher in patients with poor prognosis when compared to patients with good outcome (p=0.047, OR, 1.76, 95% CI, 1.02-3.02). No significant association of Fc-gammaRIIIb genotypes and alleles were found with GBS patients, disease severity and disease outcome. Extensive subgroup analysis revealed no significant association in genotype and allele frequencies between AMAN and AIDP subtype. In conclusion, IgG Fc-gammaR polymorphisms do not constitute significant risk markers for susceptibility to GBS, however homozygous Fc-gammaRIIa-H131 might be involved in the severe form of GBS. In addition, Fc-gammaRIIIa-F/F-158 might play an important role in the molecular mimicry against nerve gangliosides in GBS. Further studies that enroll a large number of patients (e,g. IGOS) are required to confirm the present findings from different geographical areas.

HIGH FAT FED FEMALE MICE DEVELOP PERIPHERAL NEUROPATHY DESPITE NORMAL SYSTEMIC INSULIN SIGNALING

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Peripheral neuropathy (PN) is a common complication observed in patients with impaired glucose tolerance and type 2 diabetes. Male mice fed a high fat diet (HFD) develop metabolic impairments and PN serving as an appropriate animal model to study PN development and progression. It is well documented that female mice fed a HFD display a degree of protection against HFD-induced metabolic changes with mice retaining relatively normal insulin sensitivity. This protection is attributed to differences in fat accumulation and to the anti-diabetic effects of estrogen. Based on these sex-dimorphisms we hypothesized that HFD-fed female mice would also exhibit resistance to developing PN. In the present study male and female C57BL6/J mice were fed either a standard diet (10% kcal fat; SD) or a high fat diet (60% kcal fat; HFD) from 5wk. At 16wk, 24wk and 36wk, neuropathy phenotyping was performed on all groups complemented with longitudinal metabolic assessments including insulin tolerance testing (ITT). Neuropathy phenotyping consisted of hindpaw latency to heat stimulus, motor and sensory nerve conduction velocities (NCVs), and terminal intraepidermal nerve fiber (IENF) counts. Assessment of insulin resistance through ITT demonstrated that during early HFD feeding, female HFD-fed mice exhibited relatively normal insulin responsiveness, while male HFD mice exhibited insulin resistance. Despite this finding, 16wk female HFD mice displayed a similar pattern of PN to that of their male counterparts, with similar fold-changes in hindpaw latency and sensory and motor NCVs. Therefore, although female HFD-fed mice exhibit resistance to HFD-induced metabolic changes, they display a PN comparable to male HFD-fed mice suggesting that systemic insulin resistance does not mediate PN. Further studies are underway investigating the role of insulin signaling in the peripheral nerves of female HFD-fed mice.

SELECTIVE IN VIVO REMOVAL OF PATHOGENIC ANTI-MAG AUTOANTIBODIES - A NOVEL TREATMENT OPTION FOR ANTI-MAG NEUROPATHY

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Anti-MAG (myelin-associated glycoprotein) neuropathy is a disabling autoimmune peripheral neuropathy caused by monoclonal immunoglobulin M (IgM) autoantibodies that recognize the carbohydrate epitope HNK-1 (human natural killer-1). This glycoepitope is highly expressed on adhesion molecules, such as MAG, present in myelinated nerve fibers. Since the pathogenicity and demyelinating properties of anti-MAG autoantibodies are well established, current treatments aim at a reduction of autoantibody levels. However, the therapies applied so far are primarily immunosuppressive and lack selectivity and efficacy. We therefore hypothesized that a significant improvement of the disease condition could be achieved by selectively neutralizing the pathogenic anti-MAG antibodies with carbohydrate-based ligands mimicking the natural HNK-1 glycoepitope. In an inhibition assay, a mimetic (mimHNK-1) of the natural HNK-1 epitope inhibited MAG-binding by pathogenic IgM antibodies from patient sera, however only with micromolar affinity. Therefore, considering the multivalent nature of the MAG–IgM interaction, polylysine polymers of different sizes were substituted with the mimetic. With the most promising polylysine glycopolymer $PL_{84}(mimHNK\text{-}1)_{45}$ the inhibitory effect on patient sera was improved by a factor of up to 230,000 per epitope, consequently leading to a low nanomolar

inhibitory potency. Since clinical studies indicate a correlation between the reduction of anti-MAG IgM levels and clinical improvement, an immunological surrogate mouse model for anti-MAG neuropathy, producing high levels of anti-MAG IgM, was developed. The observed efficient removal of these antibodies with the glycopolymer $PL_{84}(mimHNK\text{-}1)_{45}$ represents a first step towards an antigen-specific therapy for anti-MAG neuropathy.

ADIPOSE-NERVE SIGNALING IN PERIPHERAL NEUROPATHY

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In the United States 17% of children and young adults are obese and at risk of developing prediabetes. Prediabetic patients largely develop the same macro- and microvascular complications as patients with type 2 diabetes, including peripheral neuropathy (PN). Moreover, recent clinical data suggest normoglycemic obese patients develop PN. Central obesity, characterized by excess fat storage in visceral white adipose tissue, leads to systemic metabolic dysfunction largely due to an imbalance between pro-inflammatory/anti-inflammatory adipokine production. Subcutaneous adipose tissue is considered 'benign', but adopts a visceral-like phenotype in response to metabolic stress, with reduced thermogenicity, reduced brown adipose identity, and increased pro-inflammatory gene expression. The popliteal adipose tissue (PAT) depot, corresponding to subcutaneous adipose, is adjacent to the peripheral nerve affected in PN, contains the lymph node for lymphatic drainage of the hind limb, and expands following local, sterile hind paw inflammation. The aim of the current study was to characterize PAT changes in the high fat diet (HFD) mouse model of obesity and PN, and consider its contribution to peripheral nerve dysfunction. We previously reported C57BL6/J mice fed 60% HFD from 5-16 wk develop obesity, 'prediabetes' and PN; and switching mice back to a standard diet from 16-24 wk improves metabolic and PN phenotypes. At 16 and 24 wk PAT was bilaterally dissected and the lymph node removed. The left PAT was processed for histomorphometry, and the right PAT for RT-qPCR. At 16 wk HFD was associated with a significant shift in adipocyte size-frequency distribution, with a greater number of larger adipocytes. Switching the HFD mice back to standard chow from 16-24 wk restored the size-frequency distribution towards age-matched controls. RT-qPCR was performed to assess changes in thermogenicity (*Ucp1*), brown adipose identify (*Cidea*) and sterile inflammation (*Saa3*). At 16 and 24 wk HFD PAT had reduced thermogenicity and brown adipose identify, and increased sterile inflammation. This switch towards a visceral-like phenotype was reversed in the HFD mice switched back to standard chow. In summary, HFD-induced changes in PAT histomorphometry and adipose identity closely associate with PN phenotype. These preliminary data suggest a potential role for PAT-nerve signaling in PN.

CONSERVED BIOENERGETIC SIGNATURE IN PERIPHERAL NERVE OF BKS-DB/DB AND HIGH FAT DIET MICE WITH NEUROPATHY

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Peripheral neuropathy (PN) is a common and debilitating complication of obesity and diabetes that triggers pain and loss of sensation. Substantial nerve damage occurs in many patients prior to noticeable symptoms and no treatments are currently available; therefore, there is a critical need to identify treatment strategies that impact the underlying disease pathogenesis. Our *in vivo* fluxomics data in the BKS-*db/db* mouse model of type 2 diabetes (T2DM) and PN suggest that 'metabolic reprogramming' occurs in the T2DM nerve to downregulate mitochondrial oxidative phosphorylation of substrates derived from glycolysis and fatty acid beta-oxidation. Therefore, we hypothesize that distinct systemic metabolic alterations occur in obesity and diabetes which induce tissue-specific metabolic reprogramming within the peripheral nerve, altering fuel utilization and ultimately leading to tissue dysfunction. We contend that identifying conserved bioenergetic profiles across mouse models of PN will provide insight into key PN mechanisms. The current study utilized two mouse models of PN: the 60% High Fat Diet (HFD) mouse model of obesity and prediabetes at 20 wk of age (16 wk HFD), and the leptin receptor-deficient BKS-*db/db* model of T2DM at 24 wk of age. Mitochondrial function was determined in primary dorsal root ganglia (DRG) neurons and sural nerve tissue from both models using the Seahorse XF24 Analyzer. Resting mitochondrial oxidative metabolism was upregulated in DRG neurons from mice with PN, with increased resting ATP production and maintained mitochondrial coupling. In contrast, resting ATP generation was decreased in sural nerve from mice with PN, with decreased coupling efficiency. Relative spare respiratory capacity was attenuated in both DRG neurons and sural nerve from mice with PN, indicating that mitochondria were less able to increase respiration in response to an energetic challenge. Moreover, mitochondrial copy number was unchanged in DRG neurons, but decreased in sural nerve tissue of mice with PN compared with respective controls. These data suggest a change in absolute number and function of sural nerve mitochondria, and a conserved cross-model proximal-distal bioenergetic profile in PN. We are currently exploring the relationship between these changes and PN pathogenesis.

GUILLAIN BARRÉ SYNDROME IN A HO CHI MINH CITY, VIETNAM HOSPITAL

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Ho Chi Minh City (HCMC) is the biggest metropolitan city in southern Vietnam. Its population is more than ten million. Adult patients with neurological disorders

are seen at six city public hospitals, including 175, Hospital. There has been no systematic study of Guillain Barré syndrome (GBS) at HCMC or in Vietnam in general. We are in the process of starting a prospective GBS database that we hope to expand to the other public hospitals at HCMC. Here we describe our experience from 2016. We saw 5 GBS patients at 175, Hospital. Most of the cases were admitted in the rainy season, from late April to November, when mosquito-borne flavivirus infections are more common. Patients were seen in the first week of illness and reported antecedent fever. Two patients had diarrhea. Diagnoses were made largely on clinical features, cerebrospinal fluid analysis and nerve conduction study. Clinical findings include limb weakness, numbness and VII cranial nerve palsy. Extraocular eye movements were affected in one patient. None had respiratory involvement severe enough to require artificial ventilation or intensive care. There were no pure Miller-Fisher syndrome cases; we suspect this might be related to the mild deficits that did not prompt hospitalization. Nerve conduction studies showed typical features such as loss of F waves and abnormal blink reflex. The electrophysiology of 3 patients' was dominated by demyelinating changes, one case was largely axonal and the remaining patient had normal electrodiagnostic study. Repeat nerve conduction studies were not feasible because of limited resources. Neurologists use corticosteroids as the main treatment. Intravenous immunoglobulin and plasma exchange are costly and not reimbursed by medical insurance. We are currently preparing to systematically study GBS in southern Vietnam, specifically with regards to possible role of antecedent flavivirus infections. We are also exploring the possibility of using low volume plasma exchange as a feasible cost-effective therapeutic modality.

SUBACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY WITH TREATMENT-RELATED FLUCTUATIONS

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About 10% of patients with Guillain-Barré syndrome (GBS) treated with intravenous immunoglobulin (IVIg) or plasma exchange deteriorate after initial improvement or stabilization—a phenomenon that is termed treatment-related fluctuation (TRF). It is important to distinguish acute onset CIDP (A-CIDP) from GBS-TRF during early course of the disease, because their therapeutic strategies and prognoses are different. Herein, we describe a patient with GBS-TRF, but with an extended progression phase that exceeds 8 weeks. A 27-year-old woman was admitted due to acute onset progressive leg weakness and diplopia that had developed 2 weeks prior (onset, D0). On neurological examination, right facial palsy was also observed. Lower extremity weakness was moderate in proximal and distal muscles (MRC grade IV) with absent knee and ankle jerks. Sensory examination revealed no abnormality in all modalities. She denied any recent diarrhea or upper respiratory infection, and vaccination. Albumino-cytologic dissociation was noted in CSF analysis; white blood cell count of 3/μL and protein level of 104.2 mg/dL. Nerve conduction study revealed demyelinating sensorimotor polyneuropathy with prolonged distal latency and conduction blocks. Anti-ganglioside antibodies (GM1 IgM/G, GD1b IgM/G, and GQ1b IgM/G) were all negative. Following IVIg treatment, she was discharged with considerable improvement (D20). 11 days later, she was re-admitted due to deterioration of leg weakness and hand clumsiness (D31). After another IVIg treatment, she was discharged with clinical improvement (D49). 17 days later, however, she was admitted again (D66) due to another considerable deterioration with four extremity weakness being worst at this time (MRC grade II-IV in upper extremity, grade II in lower extremity). A-CIDP was considered given the progression phase exceeding 8 weeks, but, we decided to give another treatment with IVIg instead of a switch to corticosteroids because of uncertainty regarding distinction between A-CIDP and GBS-TRF. She was significantly improved following IVIg treatment, and finally discharged (D92). Thereafter, there has been no further deterioration during long-term follow-up of 1 year. Conclusively, this is a rare case of GBS with extended progression phase and TRF. We propose that this could be referred to as subacute inflammatory demyelinating polyradiculoneuropathy (SIDP) with TRF.

BIOMARKERS OF SMALL FIBER NEUROPATHY IN AMYLOID NEUROPATHY

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Transthyretin (TTR)-related familial amyloid polyneuropathy (FAP) constitutes a major etiology of adult-onset hereditary neuropathies worldwide, in particular, a mutant TTR of Ala97Ser (TTR-A97S) in Taiwan, the most common cause of acquired genetic neuropathy with adult onset (> 50 years of age) of Taiwanese patients. FAP is a pan-modality neuropathy involving motor, sensory, and autonomic components of the peripheral nervous system with early involvement of small fibers as a major symptom. The early symptoms of FAP are sometimes minimal and difficult to ascertain, mainly related to the fact that conventional electrophysiological examinations were not sensitive enough to detect small fiber neuropathy. Skin biopsy with quantification of intraepidermal nerve fibers (IENF) has become one of the standard approaches to diagnose small fiber sensory neuropathy based on pathological documentation of nociceptive nerve degeneration. To explore the issue of early

biomarkers in FAP, we performed skin biopsy and compared IENF density with parameters of nerve conduction studies (NCS) and quantitative sensory testing (QST) on 36 subjects (23 men, aged 55.1 ± 11.1 years) with genetic confirmation of TTR- A97S: 17 patients and 19 carriers. The IENF densities were significantly reduced compared to the age- and gender-matched controls in carriers (4.05 ± 2.01 vs. 10.39 ± 3.75 fibers/mm, p = 0.0057) and patients (0.84 ± 1.06 vs. 7.96 ± 2.39 fibers/mm, p = 0.0012). The latter was consistent with our previous report (Neurology, 75:532–538, 2010). The abnormal rate of IENF density was significantly higher than that of NCS and QST, respectively. In conclusion, there was significant skin nerve degeneration in carriers with TTR-A97S. Compared with QST and NCS, IENF density assessment had the highest abnormal rate and highest sensitivity to detect neuropathic changes in the early stage of FAP.

A NOVEL CMT2P MISSENSE MUTATION IN THE RING DOMAIN OF LRSAM1 IMPAIRS NUCLEAR TRANSLOCATION OF RNA-BINDING PROTEINS

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Charcot-Marie-Tooth type 2P (CMT2P) has been associated with frame-shift mutations in the RING domain of LRSAM1 (an E3 ligase). This study describes families with a novel missense mutation of *LRSAM1* gene and explores pathogenic mechanisms of CMT2P. This American family with dominantly inherited axonal polyneuropathy reveals a phenotype similar to those in previously reported non-US families. The affected members in our family co-segregated with a novel missense mutation Cys694Arg that alters a highly conserved cysteine in the RING domain. This mutation leads to axonal degeneration in the *in vitro* neuronal cell-line. Moreover, using protein mass spectrometry, we identified a group of RNA binding proteins (including FUS, a protein critically involved in motor neuron degeneration) that interacted with LRSAM1. The interactions were disrupted by the Cys694Arg mutation, which resulted in reduction of intranuclear RNA-binding proteins. A knockin mouse of *Cys694Arg* has been created for further explorations of CMT2P mechanisms and therapeutic development. Together, our findings suggest that the mutant LRSAM1 may aberrantly affect the formation of transcription machinery. Given a similar mechanism has been reported in motor neuron degeneration of amyotrophic lateral sclerosis, abnormalities of RNA/RNA-binding protein complex may play a role in the neuronal degeneration of CMT2P. Supported by grants from NINDS (R01NS066927) and the National Center for Advancing Translational Sciences (UL1TR000445).

RANDOMIZED CONTROLLED TRIAL OF ORAL FINGOLIMOD IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (FORCIDP TRIAL): SUBGROUP ANALYSES

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This double-blind, multicenter, parallel-group trial randomized (1:1) adult participants (N=106) with chronic inflammatory demyelinating polyradiculoneuropathy being treated with intravenous immunoglobulin (IVIg) or corticosteroids to 0.5 mg fingolimod (n=54) or placebo (n=52) once-daily. Previous treatment was discontinued (IVIg) or tapered (corticosteroids). In the total trial population, there was no significant difference between the groups in the primary outcome, time-to-first confirmed worsening (≥1-point increase on the adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] scale vs. baseline), or time-to-first any worsening (confirmed on INCAT assessment or unconfirmed). No significant difference between the two treatment groups was shown on secondary outcomes; change from baseline in grip strength and Rasch-built Overall Disability Scale (R-ODS) at six months or trial end. Analyses of pre-specified subgroups were performed for primary and secondary outcomes. Confirmed worsening in fingolimod vs. placebo-treated participants (hazard ratio, [95% confidence interval]) was analyzed by the previous treatment (IVIg, 23/41 vs. 20/41,1.28 [0.70, 2.34]; corticosteroids, 2/13 vs. 6/11, 0.26 [0.05, 1.29]), baseline INCAT score (INCAT<3, 7/23 vs.7/23, 1.19 [0.42, 3.39]; INCAT=3, 9/18 vs. 12/17, 0.62 [0.26, 1.46]; INCAT>3, 9/13 vs. 7/12, 1.24 [0.46, 3.34]), duration of CIDP (<2 years, 6/15 vs. 6/8, 0.52 [0.17, 1.62]; 2-5 years, 8/16 vs. 4/18, 3.07 [0.92, 10.22]; >5 years, 11/23 vs. 16/26, 0.67 [0.31, 1.45]), and the number of worsenings in the previous 2 years (1 worsening event, 9/22 vs. 12/23, 0.88 [0.37, 2.09]; 2 worsening events, 3/9 vs. 7/14, 0.68 [0.18, 2.64]; worsening events>2, 13/23 vs. 7/15, 1.14 [0.46, 2.87]), respectively. Hazard ratios and p-values did not show significant differences between treatment groups in any of the pre-specified subgroups.

Acknowledgments: The authors consulted for or were employed by study sponsor Novartis Pharma AG, Basel, Switzerland.

RANDOMIZED CONTROLLED TRIAL OF ORAL FINGOLIMOD IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (FORCIDP TRIAL): PRIMARY AND SECONDARY OUTCOMES

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This trial evaluated the efficacy and safety of fingolimod in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Corticosteroids, intravenous immunoglobulin (IVIg) and plasma exchange are recognized treatment options but no other immunomodulators demonstrated efficacy in a controlled trial. Fingolimod has been shown to be efficacious and is approved for the treatment of relapsing multiple sclerosis. Results from experimental autoimmune neuritis in rats suggested that it might show an effect in CIDP. In this double-blind, multicenter, parallel-group trial, CIDP participants receiving IVIg or corticosteroids were randomized to once-daily fingolimod 0.5 mg or placebo (1:1). Participants were stratified by Inflammatory Neuropathy Cause and Treatment Disability (INCAT) scores and prior treatment. Previous IVIg treatment was discontinued after one final course before randomization. Previous corticosteroid treatment was tapered over 8 weeks. The primary outcome was time-to-first confirmed worsening (≥1-point increase on the adjusted INCAT score versus baseline). Secondary outcomes included change in grip strength and Rasch-built Overall Disability Scale (R-ODS) score from baseline to Month 6 and at trial end. The trial was stopped for futility by an independent data monitoring committee after a pre-planned interim analysis based on pre-specified criteria. In all, 54 participants received fingolimod (IVIg: 41, corticosteroids: 13; age: 54.3±13.32 years [mean±standard deviation]; male: 68.5%); 52 received placebo (IVIg: 41, corticosteroids: 11; age: 54.6±11.68 years; male: 57.7%). The percentage (95% confidence interval) of participants free from confirmed worsening at the trial end was not significantly different between fingolimod (41.5% [22.7%–60.3%]) and placebo (43.2% (27.7%–58.7%); p=0.91). In the first 45 days, approximately 20% participants experienced worsening. At trial end, approximately 40% participants had no worsening. There was no significant difference after six months or at the trial end (whichever occurred earlier) in the secondary endpoints. Adverse events were reported in 41/54 and 44/52 participants in the fingolimod and placebo group, respectively. There were no deaths. Nine participants in the fingolimod group and 4 in the placebo group had serious adverse events. Adverse events leading to trial drug discontinuation occurred in 7 (13%) participants on fingolimod and none on placebo. No new safety signals emerged in this trial.
Acknowledgment: The authors consulted for or were employed by the study sponsor Novartis Pharma AG, Basel, Switzerland.

THE CRYPTIC 68-104 REGION OF MYELIN BASIC PROTEIN (MBP) CAUSES PAIN FROM LIGHT TOUCH EXCLUSIVELY IN FEMALE RODENTS: AUTOIMMUNE MECHANISMS OF SEXUAL DIMORPHISM IN MECHANICAL ALLODYNIA

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Myelin sheath enwraps non-nociceptive mechanoselective Abeta-afferents transmitting touch/vibration sense. A prominent reduction in the mechanical stimulus required to evoke a withdrawal response in rodents, a phenomena interpreted as mechanical allodynia, arises due to peripheral nerve/myelin damage. Evidence has emerged that nerve injury-induced mechanical allodynia depends on the adaptive immune/T cell activity in female but not male rodents. Having previously demonstrated both the release of the cryptic 68-104 peptide regions of myelin basic protein (MBP68-104) following sciatic nerve chronic constriction injury (CCI) and the direct, robust and T cell-dependent ability of the pure MBP68-104 peptides to induce mechanical allodynia after injection into the intact sciatic nerve, we hypothesized that MBP68-104 contributes to sexual dimorphism in mechanical allodynia. The pure MBP84-104 wild-type (WT), its histidine (His)89 mutant or scramble peptides were administered into an intact sciatic nerve fascicle in male and female rats or mice, followed by von Frey testing. Intra-sciatic MBP84-104-WT peptide induced robust and lasting allodynia in females. In contrast, males

responded with a brief and mild decline in mechanical sensitivity for one day post-injection of both wildtype and control peptides. The algesic ability of MBP84-104-WT was diminished in the His89 mutant. We here present the molecular changes in the sciatic nerve, DRG and the spinal cord after the intra-sciatic MBP84-104 injection in male and female animals. In addition, using the biotin-labeled MBP84-104 peptide and the HRP-labeled goat anti-rat IgG/IgM antibodies, we developed an ELISA to quantitatively assess seropositivity for the specific anti-MBP84-104 peptide IgM/IgG autoantibodies in female and male rats post-CCI. Human serum from female patients with multiple sclerosis was used for control. Our work corroborates the findings of sexual dimorphism of mechanical hyperpathia and suggests its potentially autoimmune nature in females.

EFFICACY OF IMMUNOGLOBULINS FOR NOD B7-2 KO MICE

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Non-obesity diabetic (NOD) B7-2 knockout (KO) mice are characterized by chronic and progressive neuritis and expected as models of immune-mediated neuropathies, especially CIDP. Hindlimb-predominant weakness due to inflammatory demyelination followed by axonal degeneration begins from around twenty week-age in all female mice until thirty week-age. To clarify the efficacy of immunoglobulins as immune-regulating therapeutics and the similarity of pathogenesis of human CIDP, we injected intraperitoneally human-derived immunoglobulins (IPIg, 20mg/mg BW/week) and saline as a control to totally forty female mice. Clinical and pathological estimations in sciatic nerves were performed in time series. As a result, the IPIg-treated group was protected from weight loss which could be related to axon loss followed by muscle atrophy as well as inflammatory demyelination between twenty-five week-age and thirty week-age compared to the control. In addition, the pathological findings in sciatic nerves showed that IPIg apparently suppressed inflammatory infiltrates. About the subsets of inflammatory infiltrates, while macrophages (CD68+) and lymphocytes (CD4+) highly existed and suggested to play a main role in the neuritis until thirty week-age, only macrophages naturally disappeared after thirty week-age without any therapeutic induction. Immunoglobulins effectively suppressed only macrophages although that did not suppress CD4+ lymphocytes. In conclusion, NOD B7-2 KO mice respond to immunoglobulins in a similar manner to human CIDP and this efficacy is due to the suppression of macrophage-dominant pathogenesis. Therefore, macrophage-derived pathogenesis is for the main target of immunoglobulin therapy and we should focus on the lymphocyte-derived pathogenesis which might plays an important role in non-responders to immunoglobulins.

CLINICOPATHOLOGICAL FEATURES AMONG CIDP SUBTYPES

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired immune-mediated polyradiculoneuropathy that is characterized by heterogeneous clinical manifestations. Typical CIDP is defined as neuropathy manifesting in a progressive manner, stepwise manner, or with recurrent symmetrical proximal and distal weakness and sensory impairment in all four limbs. Although they occur at a lower proportion than the so-called typical CIDP, atypical forms, such as multifocal acquired demyelinating sensory and motor (MADSAM), distal acquired demyelinating symmetric (DADS), pure sensory, pure motor, and focal, are considered to CIDP subtypes. Thus far, pathological features characterizing each clinical subtype have not been fully elucidated. We analyzed clinical and pathological correlations in 114 consecutive CIDP patients who underwent sural nerve biopsy and fulfilled the definite or probable EFNS/PNS criteria. There were 64 male and 50 female patients. The age at biopsy was 58.1 ± 16.1 (mean ± SD) years, and the duration from the onset of neuropathy to biopsy was 27 ± 49 months. Fifty-five percent (n = 63) of the patients were classified as having typical CIDP. Regarding atypical CIDP, MADSAM (n = 15, 13%), DADS (n = 18, 16%), and pure sensory (n = 16, 14%) subtypes were the major subtypes, while pure motor (n=1, 1%) and focal (n=1, 1%) subtypes were rare. No significant difference was found among these subtypes in terms of sex, age at biopsy, and disease duration. Sural nerve biopsy specimens revealed that the densities of large myelinated fibers significantly decreased in the MADSAM subtype than in the other subtypes (p = 0.003). In addition, the variation in nerve fibers among fascicles was more conspicuous in the MADSAM subtype than in typical CIDP (p=0.04). Patients with the DADS subtype tended to show the formation of onion-bulbs. In conclusion, pathological findings of sural nerve biopsy specimens were different among the CIDP subtypes. Further studies are needed to clarify mechanisms leading to different pathological features.

SMALL VOLUME PLASMA EXCHANGE FOR GUILLAIN-BARRE SYNDROME IN LOW INCOME COUNTRIES: A SAFETY AND FEASIBILITY STUDY

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Small volume plasma exchange (SVPE) can be an affordable and potentially effective alternative form of plasma exchange. SVPE is the repeated removal of small volumes of supernatant plasma over several days via sedimentation of patient whole blood. The aim of this study is to assess the clinical feasibility and safety of SVPE in patients with GBS in low-income countries. Twenty adult patients with GBS diagnosed as per the criteria for GBS of the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) were enrolled for SVPE at a centre in Bangladesh. Serious adverse events (SAE) were defined as the number of patients developing severe sepsis associated with the central venous catheter (CVC) or deep venous thrombosis in the limb where the CVC is placed for SVPE. The SVPE procedure was considered safe if less than 5 of 20 SVPE-treated GBS patients have a SAE, and feasible if eight litres of plasma could be removed in at least 15 of 20 SVPE-treated GBS patients. Among the 20 cases who received SVPE, 13(65%) patients were male and the age range between 19 to 55 yrs. All the patients were quadriplegic and bedbound at enrolment for SVPE with a median MRC score of 20 (IQR, 0 - 29). Cranial nerve involvement, autonomic dysfunction and requirement for assisted ventilation were observed in 11(55%), 9(45%) and 3(15%) patients respectively. Electro physiologically 15(75%) patients were motor axonal and 5(25%) patients were sensory-motor demyelinating type. During the SVPE none of our patients experienced SAE and one patient experienced central line associated blood stream infection. Common adverse effects were transient intravenous fluid responsive hypotension during the SVPE sessions in 10(50%), CV catheter insertion site hemorrhage in 10 (50%) and hypersensitivity reaction to fresh frozen plasma in 5(25%) patients. There was no hypo-albuminemia, anemia or electrolyte imbalance observed in most patients (95%) treated with SVPE. Improvement in one or more grade of the GBS disability score at four weeks after the onset of SVPE was observed in 14(70%) patients. In conclusion SVPE can be a safe, feasible and cost effective alternative to standard PE in the developing countries.

GUILLAIN BARRÉ SYNDROME IN BANGLADESH: PAST, PRESENT AND FUTURE PERSPECTIVE

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Guillain-Barré syndrome (GBS) is a descriptive disease entity defined by a set of clinical, electrophysiological and laboratory criteria. Various clinical phenotypes exist that may be triggered by different antecedent infectious events. Although the disease appears to affect primarily the elderly in developed countries, but, scenario is different in developing countries. Bangladesh has made an impressive progress towards the eradication of poliomyelitis, and no new cases have been reported since 2000. GBS, an acute polyradiculoneuropathy, is the most frequent cause of acute flaccid paralyis. The crude incidence rate of GBS in <15 years of age reported here appears to be 2.5× to 4× higher than that reported in the literature. We conducted a hospital based observational study including 600 patients fulfilling the National Institute of Neurological Disorders and stroke (NINDS) criteria for GBS patients between 2010 and 2016 in Dhaka Medical College Hospital, Dhaka, Bangladesh. Detailed clinical, electrophysiological, serologic and microbiological data were obtained. GBS affected predominantly in young adults males (M/F=2:1) living in rural areas. Antecedent events were recorded in >70% of patients; frequent events being gastroenteritis (>40%) and upper respiratory tract infection (18%). More than 60% of the patients were bed-bound (GBS disability score 4) at entry and about 20% patients required mechanical ventilator. About 90% patients did not receive specific treatment either Intravenous Immunoglobulin (IVIg) or plasmapheresis due to high expensive treatment cost. 13% patients had died during hospitalization. 60% of patients had an axonal variant of GBS and evidence for a recent *C. jejuni* infection (55%). *C. jejuni* infection was significantly associated with serum antibodies to the gangliosides GM1 and GD1a, axonal neuropathy, and greater disability. In conclusion, the majority of the patients do not receive standard treatment with IVIg in view of its high price. Therefore, we developed low-cost treatment strategies and conducted a safety and feasibility trials for small volume plasma exchange (SVPE) on GBS patients in Bangladesh. In future, it is essential to conduct a phase II clinical trial to assess the efficacy of SVPE for low-in-come countries.

DOES INTRAVENOUS IMMUNOGLOBULIN SERVE AS AN EFFECTIVE TREATMENT FOR GUILLAIN-BARRÉ SYNDROME IN DEVELOPING COUNTRIES? A CONTROLLED MATCHED PAIR ANALYSIS

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Prognosis of Guillain-Barré syndrome (GBS) has not improved in last two decades. Current therapies

(Intravenous immunoglobulin, IVIg and plasma exchange, PE) had been proved to be effective on two third of patients in developed world. Unpredictable and poorly understood clinical course of GBS hamper treatment development. In Bangladesh, most patients affected by GBS cannot afford specific treatments with IVIg or PE instead most of them receive only supportive care. Therefore, we aimed to compare the outcome of IVIg treated patients with supportive care patients in improvement of GBS disability score and MRC sum score by using world's largest GBS cohort in Bangladesh. We conducted a prospective observational study enrolling 600 GBS patients between 2010 and 2016 from Dhaka Medical College Hospital and National Institute of Neuroscience and Hospital, Dhaka, Bangladesh. Only 53 GBS patients (9%) received standard IVIg treatment. In current analysis, 53 IVIg treated patients and 53 age, sex and severity matched controls (supportive care only) were considered. Outcome of both groups were compared using Fisher's exact or Chi square test and survival analysis were performed by Kaplan Meier method using log rank test. Among 106 patients (cases and controls), male/female (62/44), median age 19 years, 60% patients were bed-bound, one-fourth patients required mechanical ventilation and 63% were axonal. We did not found any significant differences of treatment outcome in both cases and control groups in GBS disability score (Week 4: p=0.82, 6 months: p=0.84) and MRC sum score (Week 4: p=0.71, 6 months: p=0.86). Survival analysis revealed, the differences of time required for independent locomotion, improvement of one GBS disability score and improvement of MRC score were not statistically significant between treatments (IVIg) and supportive care patients. In conclusion, our analysis showed that standard dose of IVIg use has no considerable advantage to improve specific outcome measures among GBS patients in Bangladesh. As the phenotype of GBS in Bangladesh is different from developed world; therefore, an efficacy trial for IVIg is needed for developing countries like Bangladesh or new targeted therapeutic strategies can append beneficial effects for GBS patients.

PAIN-RELATED SEP AFTER SELECTIVE A-DELTA- AND C-FIBER STIMULATION IN PATIENTS WITH NEUROPATHIC PAIN AND ITS POST-TREATMENT CHANGES

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Diabetic neuropathy is a frequent cause of neuropathic pain, suggesting the small-fiber involvement. Additionally, persistent peripheral pain-related inputs could cause neuronal hyperexcitability and complex interactions of the nociceptive pathways, i.e., central sensitization. To investigate the pathophysiology of neuropathic pain in diabetic neuropathy, we studied pain-related evoked potentials (PREPs) after selective intraepidermal electrical stimulation (IES) to A-delta- and C-fibers in diabetes patients with neuropathic pain (n=24) and without neuropathic pain (n=20). We also conducted a longitudinal study to assess changes in PREPs and pain profiles in patients with neuropathic pain 3 months after the start of treatment with duloxetine. This study is registered with the UMIN Clinical Trials Registry, UMIN000017130.
IES was applied in the hand and foot, and PREPs were recorded from the Cz electrode referenced to the linked earlobes. We evaluated PREP latencies, amplitudes, and amplitude ratios of PREPs after C/A-delta -fiber stimulation. In the conventional nerve conduction studies, patients with neuropathic pain significantly showed conduction slowing and decreased SNAP amplitudes in the median and sural nerves compared with those in patients without neuropathic pain. In pain-related SEP studies, there were no significant differences in PREP amplitudes and latencies after A-delta - or C- fiber stimulation between the patients with neuropathic pain and without it. PREP amplitude ratios after C/A-delta -fiber stimulation tended to increase in patients with neuropathic pain compared to patients without pain. After the treatment with duloxetine, C/A-delta -PREP amplitude ratios were significantly decreased after both hand and foot stimulation, and as for numerical rating scale (NRS) scores as the intensity of pain. Patients with less pain relief showed the tendency of higher C/A-delta PREP amplitude ratios before treatment compared to patients with better pain relief. The correlation between reduction of C/A-delta PREP amplitude ratios and NRS reduction did not reach statistical significance. This pain-related SEP study demonstrated that abnormal cortical response in patients with neuropathic pain could improve after the treatment with duloxetine, this might reflect the cortical hyperexcitability as a central sensitization.

Declaration of conflict of interest
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VOLUNTARY EXERCISE MODULATES MACROPHAGE POLARIZATION FOLLOWING SCIATIC NERVE INJURY AND IMPROVES FUNCTIONAL RECOVERY IN MICE

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Peripheral nerve injury is commonly associated with traumatic injury which is often amenable to surgery. Despite improved methods in surgical repair, functional recovery remains a challenging clinical problem that often leads to significant morbidity in patients. Alternative therapies that could augment surgical repair may be beneficial in functional outcomes. Neuroinflammation is a complex pathway with different cellular components and cytokines that are activated following peripheral nerve injury. Macrophages are responsible for the breakdown of

debris following injury as well as promotion of regenerative signals. Macrophage polarization is the process by which macrophages take on phenotypically distinct functions based on the local environment and signaling cues. Exercise has been shown to drive macrophage polarization from a pro-inflammatory M1 phenotype towards an anti-inflammatory M2 phenotype in numerous tissues, but remains uninvestigated in the peripheral nervous system. The purpose of our study was to identify how exercise affects macrophage polarization, motor and sensory function, and neuroregeneration following sciatic nerve crush. C57BL/6 mice underwent sciatic nerve crush injury and were then given access to running wheels (exercised) or not given access to running wheels (sedentary) for 4 weeks. Exercised mice ran an average of 2.9 km per night. Injured exercised mice were protected from the development of thermal hyperalgesia when compared to injured sedentary mice. Exercised mice had fewer paw slips on beam walk testing compared to sedentary mice. No differences were measured in mechanical sensitivity or motor coordination and balance assessed by Rotarod. While motor nerve conduction velocities were significantly reduced for injured mice compared to uninjured controls, motor nerve conduction velocities from injured exercised animals were significantly higher than injured sedentary animals suggesting improved nerve recovery with exercise. Injured sciatic nerves from exercised mice demonstrated increased M2 macrophages compared to sciatic nerves from injured sedentary mice. The behavioral changes and altered macrophage polarization correlated with increased epidermal nerve fiber density, improved myelination, and increased *in vitro* neurite outgrowth from injured exercised animals. Therefore, exercise alters macrophage polarization towards an anti-inflammatory phenotype which improves repair and recovery of the injured peripheral nerve.

THE USE OF MAGNETIC RESONANCE NEUROGRAPHY IN PERIPHERAL NERVE SHEATH TUMORS

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Diffusion tensor imaging (DTI) has long been used to evaluate the location and integrity of white matter tracts in the brain. DTI uses quantitative data and directionality of water diffusion to determine axonal connectivity of the nervous system. The technology has only recently been utilized in limited settings in the peripheral nervous system due to challenging technical factors and lack of widespread availability. Magnetic Resonance (MR) neurography or peripheral neurography is a technique which uses diffusion to differentiate between intraneural and perineural tissues. It allows for fascicle patterns to be visualized particularly in the setting of peripheral nerve sheath tumors. Peripheral nerve sheath tumors of various pathologies cause surrounding nerves to be involved or displaced in a range of directions. This technique helps determine the anatomic location of these nerve fibers in relation to the mass, which is particularly helpful at distinguishing neuromas from schwannomas. This data is invaluable to the surgeon to ensure a safe and low morbidity operation. While this technology has benefit particularly with surgical planning, it has been underutilized due to the challenges of requiring complex software to produce fiber tracks and the inability to translate these images into the operating room. Here, we utilized BrainLab software that is commonly available and utilized in surgical suites to produce images of the radial nerve fiber tracts with an associated peripheral nerve sheath tumor prior to surgical resection. While the software is commonly used in the central nervous system, it has not been reported to have been used in the peripheral nervous system. This software offers a high usability and produces anatomically correct and reliable fiber tracts. This technique overcomes the reliance on highly specialized software and extensive training required for use that most other tractography software has. Utilizing peripheral neurography in this case allowed for complete surgical resection without postoperative deficits. This data offers clinicians an option to investigate peripheral nerve fibers in various pathologic states, to plan appropriate operative trajectories to peripheral nerve pathology, and to improve surgical outcomes for patients with peripheral nerve sheath tumors.

RITUXIMAB IN INTRACTABLE CIDP

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune mediated neuropathy that is responsive to immunomodulatory agents such as glucocorticoids, intravenous immunoglobulin (IVIg) and plasma exchange (PE). The specific immunopathogenic mechanisms of CIDP remain unclear but there is increasing interest in nodal proteins as a site of the immune attack. Even though the majority of patients respond to one of the aforementioned immunomodulatory agents there are some who are unresponsive or incompletely responsive to these first line agents and other more aggressive treatments may be necessary. Cyclophosphamide and stem cell transplantation may be effective but are associated with considerable morbidity. Anecdotal reports suggest that rituximab may be beneficial for some patients that fail first-line therapy, especially if they have antibodies to nodal proteins. We present four patients with intractable CIDP who responded to rituximab. One of the three patients had diabetes. Disease duration prior to starting rituxan was short (4 months) in two patients and longer 24 and 27 months in the other two. All patients had failed treatment with glucocorticoids and IVIg, and in two, plasma exchange and IVIg-PE were also ineffective. Two of the four patients were quadriparetic and non-ambulatory. Two 1 gm doses two weeks apart of intravenous rituximab were instituted in all patients. All patient tolerated the treatments well without adverse effects. All patients responded within four

weeks and continued to improve at six months. Other immunomodulatory agents were successfully tapered but not totally discontinued. It remains unclear whether antibodies to nodal proteins were present in these patients. In conclusion, although rituximab efficacy remains uncertain on the basis of randomized controlled clinical trials, it may be beneficial in selected patients otherwise intractable to first-line treatments. Further studies are necessary to better understand which patients may benefit most from rituximab and where in the treatment algorithm rituximab should be applied.

THE FORGOTTON CELL TYPE IN NEUROPATHIC PAIN: SATELLITE GLIAL CELLS

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Neuropathic pain is a chronic condition seen in patients suffering a direct injury to the peripheral or central nervous system or an indirect injury due to, e.g., diabetes or multiple sclerosis. Current treatment options fall short of preventing or completely relieving patients of their pain. For years, research has focused on understanding the role of neurons in neuropathic pain pathogenesis while overlooking the role of supportive cells in general and satellite glial cells (SGCs) in the dorsal root ganglion in particular. These cells not only buffer the neuronal microenvironment they are also involved in controlling the electrical activity flowing through the neurons and in neuropathic pain pathogenesis. The aim of this project is to understand the role of SGCs in neuropathic pain development and thereby aid the identification of new drug targets. To purify the SGCs from adult mice we optimized a fluorescently activated cell sorting (FACS) protocol. The success of our purification method was confirmed using qRT-PCR and visual inspection of the sorted cells. Finally, we are running RNA sequencing on SGCs after peripheral nerve injury to compare their transcriptome to that of uninjured cells at different time points. The results from our study are likely to deepen our understanding of how SGCs contribute to the development and maintenance of neuropathic pain.

FUNCTIONAL *FAS/FASL* PROMOTER POLYMORPHISMS ASSOCIATED WITH INCREASED RISK OF NERVE DAMAGE IN GUILLAIN–BARRE´ SYNDROME IN BANGLADESH

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Guillain–Barre´ syndrome (GBS) is an immune-mediated disorder in the peripheral nervous system (PNS) triggered by molecular mimicry against nerve gangliosides. One of the cell surface receptors (Fas)-ligand (FasL) interaction transmits apoptotic signal to eliminate the auto-reactive B and T-cells, which generates cross-reactive antibody against nerve cells. Host genetic polymorphism of Fas and FasL may alter their expression and induce aberrant apoptotic response to develop GBS. Therefore, we determined the single nucleotide polymorphisms (SNPs) of both Fas receptor (-1377G/A and -670A/G) and FasL ligand (-843C/T) in GBS patients (N=100) as well as healthy controls (N=97) using the LightCycler technique. Serum level of soluble form of Fas and FasL was measured using commercially available sandwich ELISA kit. Comparison of genotype, allele and haplotype frequencies was done with the GBS subgroups based on the clinical and serological data. AG heterozygote (p=0.0494, OR=2.5, 95% CI=1.03-6.1) and polymorphic G-allele (p=0.0387, OR=1.9, 95% CI=1.1-3.5) of Fas receptor -670A/G promoter SNPs were significantly associated with anti-ganglioside (GM1) antibody positive GBS patients. In addition, -670G-allele (p=0.02, OR=4.8, 95% CI=1.3-17.4) and -1377G/-670G haplotype (p=0.0251, OR=4.833, 95% CI=1.3-18.04) were predominantly associated with the axonal variant of GBS patients. Serum soluble form of sFas (median levels 259 pg/ml vs. 221 pg/ml, p=0.0373) and sFasL (median levels 260 pg/ml vs. 202 pg/ml, p=0.0528) were found to be elevated in anti-GM1 antibody positive GBS patients compared to anti-GM1 negative patients. No significant association was found in genotypic distribution between GBS patients and healthy controls. In conclusion, Fas/FasL promoter SNPs are not a susceptible factor for GBS but could be one of the influencing factors to develop cross-reactive anti-ganglioside antibodies in GBS patients in Bangladesh. Furthermore, functional studies with a larger sample size (using cohort like International GBS outcome studies-IGOS) are required to explain the immune pathogenic role of these SNPs for GBS patients.

AUTOPHAGOLYSOSOME-MEDIATED MYELIN CORPSE FORMATION BY SCHWANN CELLS IN SEGMENTAL DEMYELINATION

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Myelination is essential for the proper function of the nervous system. Schwann cells, which form the peripheral myelin sheath, have the unique ability to dedifferentiate and to destroy the myelin sheath under various demyelination conditions. During Schwann cell dedifferentiation-associated

demyelination in Wallerian degeneration after axonal injury, Schwann cells exhibit myelin and junctional instability, down-regulation of myelin gene expression and autophagic myelin decomposition. However, in inflammatory demyelinating neuropathy, it is still unclear how Schwann cells react and contribute to segmental demyelination before myelin scavengers, macrophages, are activated for myelin clearance. Here, we show that Schwann cell dedifferentiation-associated demyelination is a mechanism involved in the initial demyelination observed in a mouse model of inflammatory demyelinating neuropathy using ultrastructural, biochemical and microarray analyses. Myelin uncompaction and myelin membrane instability generated by dedifferentiated Schwann cells lead to autophagolysosome-dependent cytoplasmic amputation between the axon-containing myelin sheath and the Schwann cell body, resulting in the formation of the "myelin corpse", thereby allowing macrophages to phagocytose the myelin corpse in the end stage of segmental demyelination. We found myelin corpse formation in inflammatory demyelination to be a process similar to the myelin rejection during Wallerian degeneration, which appeared to be dependent on Schwann cell autophagolysosome activation since Schwann cell-specific *Atg7* knockout mice exhibited delayed myelin rejection following nerve injury. Finally, lysosome inhibition in Schwann cells not only prevented segmental demyelination but also delayed the progression of clinical stages by suppressing the myelin corpse formation in inflammatory demyelinating neuropathy. Thus, our findings indicate that demyelination by Schwann cells and macrophages might be part of a process that includes sequential divisions of labor with respect to myelin rejection and digestion, respectively. In conjunction with previous studies showing Schwann cell dedifferentiation and autophagy in toxic and hereditary neuropathies, the concept of "Schwann cell dedifferentiation-Associated Demyelination" provides insight into the development of possible therapeutic strategies to prevent Schwann cell demyelination in peripheral demyelinating neuropathies.

CHARCOT MARIE TOOTH DISEASE TYPE 4C: NOVEL MUTATIONS, CLINICAL PRESENTATIONS, AND DIAGNOSTIC CHALLENGES OF AN ATYPICAL CMT

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Objective: To analyze and describe atypical presentations of CMT4C.
Methods: We present clinical and physiologic features of five subjects with CMT4C caused by biallelic private mutations of *SH3TC2*.
Results: All cases manifested scoliosis and nerve conduction studies in the demyelinating range. All exhibited signs of motor impairment within the first years of life. We describe two or more different genetic diseases in the same patient, atypical presentations of CMT and 3 new mutations in CMT4C patients.
Discussion: A new era of unbiased genetic testing has led to this small case series of individuals with CMT4C, and highlights the recognition of different genetic diseases in CMT4C patients for accurate diagnosis, genetic risk identification and therapeutic intervention. The phenotype of CMT4C, in addition, appears to be enriched by a number of features unusual for the broad CMT category.

CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: INFLUENCE OF BODY MASS INDEX ON NERVE CONDUCTION STUDIES AND ON THE CHARCOT MARIE TOOTH EXAM SCORE

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Introduction: Charcot-Marie-Tooth Disease Type 1A (CMT1A) is caused by a duplication of the peripheral myelin protein 22 gene at chromosome 17p11.2-12. Whether body mass index (BMI) affects electrophysiological or clinical data for CMT1A patients is not clear because the relevant data are limited.
Methods: Electrophysiological data, the Charcot Marie Tooth exam score (CMTES), and BMI from 112 patients with known CMT1A were obtained and analyzed.
Results: When controlled for age, BMI does not affect studies of ulnar motor nerve conduction in CTM1A patients, but rather specific components of the CMT exam scores (CMTES, loss of pinprick sensation and motor strength in the lower extremities).
Discussion: BMI and clinical components of the CMTES are correlated, but it is uncertain which is the primary effect – i.e., whether the reductions in pinprick sensation and motor strength in the lower extremities lead to a higher BMI, or higher BMI results in these signs.

CHARCOT-MARIE-TOOTH DISEASE TYPE 1C: CLINICAL AND ELECTROPHYSIOLOGICAL FINDINGS FOR THE C.334G>A (P.GLY112SER) *LITAF/SIMPLE* MUTATION

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Introduction: Charcot-Marie-Tooth Disease type 1 C (CMT1C) is a rare, dominantly inherited neuropathy caused by mutations in the lipopolysaccharide-induced tumor necrosis factor *(LITAF)* or small integral membrane protein of the lysosome/late endosome (*SIMPLE*) gene.
Methods: We present a case series comprised of 10 patients in whom CMT1C is caused by a Gly112Ser substitution in the encoded protein. We focus on clinical presentation, electrodiagnostic analyses, and our findings in the context of previously described cases.
Results: The Gly112Ser mutation causing CMT1C is a mild form of CMT, as patients walked on time, had less weakness than those with Charcot-Marie-Tooth Disease type 1A (CMT1A), had a Charcot Marie Tooth neuropathy score (CMTNS) indicative of mild disease, and had faster ulnar and median motor nerve conduction velocities compared to those with CMT1A.
Discussion: The G112S mutation in *LITAF* seems to be clinically indistinguishable from a mild presentation of CMT1A.

CRITICAL ROLE FOR MONOCARBOXYLATE TRANSPORTER (MCT1) IN DEVELOPING AND REGENERATING PERIPHERAL NERVES

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Peripheral nerves are highly dependent on metabolic energy to maintain both basic cellular functions such as axon transport, Na+/K+ ion gradients, and myelination, as well as to support regeneration following injury. Though glucose certainly provides some metabolic support, our recent studies have shown that monocarboxylates, such as lactate, pyruvate, and ketone bodies, also contribute to recovery from peripheral nerve injury. Monocarboxylate transporters, particularly MCT1, are the predominate transporters for monocarboxylates in the peripheral nerve. In a recent publication, we found that MCT1 heterozygous null mice, which express 50% less MCT1 in all cells, have slowed nerve regeneration and reduced myelination following sciatic nerve crush. This study was limited by the global reduction of MCT1, which is widely expressed in Schwann cells (SC), dorsal root ganglia (DRG) neurons, endothelial cells, macrophages, and perineurial cells within the regenerating peripheral nerve. To better understand the mechanism by which MCT1 contributes to normal nerve function and nerve regeneration, we produced and validated conditional MCT1 null (MCT1LoxP) mice that allow selective deletion of MCT1 from SCs, DRG neurons, endothelial cells, or macrophages through mating to cell-specific Cre lines. We are currently quantifying peripheral nerve development, aging, and regeneration in each of these mouse lines. Following SC-, but not DRG-, specific MCT1 knockdown, sensory peripheral nerves develop demyelination by 4 months of age, manifest by reduced myelin thickness, increased *g*-ratio, and reduced conduction velocity. Studies are ongoing in cultured SCs to determine the mechanism for demyelination. Neither SC nor DRG knockdown of MCT1 impairs nerve regeneration following sciatic nerve crush. These results suggest that SC-specific MCT1 is critical for maintaining myelin in sensory, but not motor, peripheral nerves as they age. They also suggest that MCT1 expression in peripheral nerve cell types, other than SC and DRG, is important for nerve regeneration. Ongoing studies are determining the contribution of MCT1 in other peripheral nerve cell types, particularly endothelial cells and macrophages, to normal development and regeneration following injury. Our results will clarify the role of lactate and its transporter, MCT1, in peripheral nerve function, potentially suggesting novel targets for demyelinating neuropathies or nerve injuries.

DIGIT WRINKLE SCAN©: FROM NORMATIVE VALUES TO ITS CLINICAL APPLICABILITY IN SMALL FIBER NEUROPATHY

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Small fiber neuropathy (SFN) is a condition in which the smallest nerve fibers are affected, characterized by neuropathic pain and autonomic dysfunction. According to international criteria, SFN diagnosis is based on clinical symptoms in combination with abnormal temperature threshold testing (TTT) and/or reduced intraepidermal nerve fiber density (IENFD) in skin biopsy. Skin biopsy is moderately sensitive, invasive and the process is time consuming and expensive. TTT is a widely available diagnostic tool, but lacks specificity. Previous studies introduced stimulated skin wrinkling (SSW) as an objective, non-invasive diagnostic tool to detect sympathetic nerve dysfunction in SFN by means of a categorical assessment. However, our unpublished data has shown that inter-observer reliability of categorically assessed SSW is quite low. In this current study we will use a new digital method for SSW quantification: the Digit Wrinkle Scan© (DWS©). The primary study objective is to define normative values for DWS© expressed as total wrinkle length per fingertip surface (mm/mm2). Subsequently we investigate the applicability of DWS© in patients with definite SFN, based on abnormal IEFND and/or TTT, determining the DWS© sensitivity and specificity, as well as its validity. For this cross-sectional study, we will include 60 healthy participants and 200 patients diagnosed with SFN. Eligibility is based on meeting the inclusion and exclusion criteria and providing written informed consent. Skin wrinkling is induced by EMLA (eutectic mixture of local anesthetics) cream© application and captured by taking pictures. The primary outcome measure is total length of wrinkles per mm2 as shown on the photographs, which will be calculated by a new software program. Patients are stratified according to age and gender. Based on the results of healthy participants, normative values will be defined. Inter- and intra-observer reliability will be

determined. In the SFN group, additional correlation analysis will be conducted to determine the correlation between DWS© and different outcome measures (SFN-Symptom Inventory Questionnaire, visual analogue pain scale, neuropathic pain scale, SFN- Rasch-built Overall Disability Scale, IENFD and TTT). We expect to provide digitally quantified SSW (dSSW©) normative values that can be used in clinical practice in the diagnostic workup for SFN.

IDENTIFICATION OF COMMON MOLEUCLAR PLAYERS INVOLVED IN THE PROGNOSIS AND PATHOGENESIS OF AXONAL CMT SUBTYPES

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CMT2, characterized by axonal degeneration, is an inherited motor and sensory neuropathy accounting for about 20% of total CMT patients. The CMT2 subtype shows on its own, a vast genetic heterogeneity with more than 140 mutations in 26 known genes rendering the identification of relevant drug targets and therapies very challenging. So far, only HDAC inhibitors have shown promising results in mouse models for HSPB1 mediated axonal CMT (CMT2F), albeit such a single gene approach may have a limited relevance at clinical levels owing to the limited number of patients per genotype. In this study, we investigated common causative molecular players of CMT2 associated axonal degeneration. For this, an iTRAQ based proteome analysis was performed on five patient's derived lymphoblasts bearing different CMT2 causal mutations alongwith respective age and gender matched unaffected controls. Software-assisted interpretations of the obtained data led us to identify two proteins which were significantly downregulated in CMT2 patients compared to controls. These two proteins were then validated using Western blotting and qPCR on patient derived lymphoblasts and fibroblasts. Our results prompted us to unveil whether these two proteins can be used as potential biomarkers for identifying CMT2 patients. Therefore, through a Europe-wide collaboration, we constructed a cohort of 43 CMT2 patients and 21 healthy controls. These two proteins exhibited significant downregulation in this cohort suggesting a potential new role of these proteins as CMT2 biomarkers. Remarkably, we were also able to validate the significant decrease in iNeurons (neurons differentiated from patient derived iPSCs) strengthening the importance of our finding and also suggesting the relevance of these proteins in the pathogensis of axonal CMT. This will be the first study involving multiple CMT causal genes at once, thereby holding the potential to offer new drug targets and potential biomarkers with wider application both clinically and pharmaceutically.

RESTORATION OF NEUROMUSCULAR FUCTION IN A MOUSE MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A BY DIFFERENTIATED HUMAN TONSIL-DERIVED MEESENCHYMAL STEM CELLS

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Mesenchymal stem cells (MSCs) represents a valuable source of stem cell therapy, can differentiate into various cell types. We investigated of the neuromuscular potential of human tonsil-derived MSCs (T-MSCs) for neuromuscular regeneration in trembler-j mice that is considered to be a model for Charcot-Marie-Tooth disease type 1A (CMT1A diseases), which is involving hereditary motor and sensory peripheral neuropathies. The T-MSCs differentiated toward skeletal myocytes, as evidenced by increased expression of skeletal muscle-related markers (including troponin I type 1, and myogenin) and the formation of myotubes *in vitro*. *In situ* transplantation of T-MSC-derived myocytes (T-myocytes) into gastrocnemius in *trembler*-j mice, a mouse model of CMT1A, enhanced motor function, as identified with recovery by a compound muscle action potential (CMAP) amplitude. And the regenerated shape of the sciatic nerve and skeletal muscle by immunochemistry, without the formation of teratomas. Furthermore, the expression levels of nerve growth factor (NGF) and glial cell line-derived neurotrophic factor (GDNF) were significantly increased in T-myocyte compared with T-MSCs *in vitro*. These results indicate that the transplantation of T-myocyte can be a therapeutic option of cell therapy for the neuromuscular regeneration in hereditary peripheral neuropathy, comprising CMT1A disease.

INTRATHECAL GENE THERAPY IN DIFFERENT MUTANT MOUSE MODELS OF CMT1X

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X-linked Charcot-Marie-Tooth disease (CMT1X) is a common form of inherited demyelinating peripheral neuropathy resulting from mutations affecting the gap junction protein connexin32 (Cx32). Using a Cx32 knockout (KO) mouse model of the disease, we have shown that targeted expression of virally delivered Cx32 results in morphological and functional

improvement. Since patients with CMT1X express mutant forms of Cx32 in Schwann cells, that could potentially interact with virally delivered wild type (WT) Cx32 through dominant-negative effects, we also treated mutant mice expressing the T55I, R75W and N175D mutations associated with CMT1X on a Cx32 KO background. All three mutants were localized in the perinuclear compartment of myelinating Schwann cells consistent with retention in the ER (T55I) or Golgi (R75W, N175D) with loss of physiological expression in non-compact myelin areas. Following intrathecal delivery of the human *GJB1* gene we could detect the virally delivered WT Cx32 correctly localized in the non-compact myelin areas only in T55I/Cx32KO mutant mice, but not in the other two mutants, suggesting dominant effects of the R75W and N175D mutant but not of the T55I mutant. *GJB1* treated T55I/Cx32 KO mice showed improved motor performance, along with lower ratios of abnormally myelinated fibers and reduced numbers of inflammatory cells in all tissues examined compared to mock-treated animals. In contrast, *GJB1* treated R75W and N175D mutant mice showed only slight but not statistically significant improvement. This study provides additional proof of principle for a clinically translatable gene therapy to treat CMT1X even in the presence of endogenously expressed Cx32 mutants, since at least one ER-retained Cx32 mutant did not interfere with the expression of virally delivered Cx32 allowing a therapeutic benefit similar to Cx32 KO mice. However, Golgi-retained mutants may interfere with virally delivered WT Cx32 and other approaches besides gene addition may be needed for effective treatment.

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ANTIBODIES TO NEUROFASCIN155 IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: DIAGNOSTIC UTILITY OF A CONVENTIONAL ASSAY

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Antibodies to a glial protein, neurofascin (NF)155 have recently been identified in approximately 10% of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), which are IgG4-predominant. IgG4 anti-NF155-associated CIDP may be a distinct subtype from typical CIDP in terms of clinical features and response to immunotherapy. However, a diagnostic criterion of anti-NF155-associated CIDP has not established yet. To develop optimal criteria and design the best treatment plan for the anti-NF155-associated CIDP, procedures for determining anti-NF155 antibodies should be simplified, prevalent, and reproducible, as well as being accurate. Cell-based assay (CBA) has hitherto been utilized for determining antibodies to NF155 in sera from patients, results of which have been confirmed by immunohistochemistry (IHC) using teased nerve fibers from rodents. These methods are the most reliable techniques, while not necessarily easy-to-use and easy to maintain in most laboratories. In the present study, we aimed to validate the diagnostic utility of a conventional enzyme-linked immunosorbent assay (ELISA) for determination of anti-NF155 antibodies and the IgG subclass. Sera from 191 patients with EFNS/PNS criteria-met CIDP were examined with ELISA using human recombinant NF155. To verify ELISA results, IHC on rat sciatic nerves, western blot (WB) and CBA using NF155-transfected and naive HEK293 cells were conducted. The human NF155-based ELISA clearly distinguished between anti-NF155 antibody-positive and -negative sera. Fifteen CIDP patients (8%) were IgG4 anti-NF155 antibody-positive, which were confirmed by WB, IHC and CBA studies. None of disease controls or healthy subjects had positive results. Twenty-five sera randomly selected from 176 anti-NF155-negative CIDP sera were also negative on CBA. The anti-NF155 activities on ELISA were significantly positively-correlated with those on CBA ($p < 0.01$). Analyses of clinical and laboratory findings showed that anti-NF155-associated CIDP was characterized by younger onset, distal dominant phenotype, tremor, sensory ataxia, higher protein levels in cerebrospinal fluid, and poor response to IVIg, which were consistent with those in previous studies. This ELISA combined with determination of the IgG4 subclass is a simple and reliable method for initial screening for anti-NF155 antibodies.

CLINICAL AND NEUROPHYSIOLOGICAL PROFILE OF CMTX3 IN CHILDHOOD

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The genetic abnormality responsible for X-linked Charcot-Marie-Toothy neuropathy subtype CMTX3 was recently identified by whole genome sequencing to be a 78 kb insertion into chromosome Xq27.1. The clinical profile of CMTX3 in childhood is not well described. We reviewed the clinical characteristics, neurophysiological profile and CMT Pediatric Scale (CMTPedS) assessments of 11 children with genetically confirmed CMTX3. CMTX3 was characterized by early onset, and early and progressive hand weakness. Most affected children were symptomatic within the first two years of life. The most common presentation was with equinovarus foot deformity in the first year of life. CMTPedS analysis in these children revealed that CMTX3 progressed more rapidly (4.3 ± 4.1 points/2 year, n=7) than CMT1A and CMTX1. Grip strength in the second decade of life in most affected males was two standard deviations below age- and sex-matched normative reference values. The most severely affected individual was wheelchair bound at 14 years of age and two individuals had no movement in the small muscles of the hand in the second decade of life. There was only a single symptomatic female identified and she had mild signs. Nerve conduction studies showed a demyelinating sensorimotor neuropathy with motor conduction velocity in eight children while one child had a length-dependent sensorimotor axonal neuropathy. Understanding the unique phenotype of CMTX3 is essential for directing genetic testing, as the CMTX3 insertion will not be detected on the SNP microarrays, multi-gene panels or whole-exome sequencing currently used for the diagnosis of CMT. The early onset of disease coupled with rapid progression means that many children with CMTX3 will have severe disability within the first two decades of life and hence early diagnosis is needed for early commencement of rehabilitation.

THE SUCCESSFUL USE OF VERY HIGH DOSE IVIG IN ACQUIRED, DEMYELINATING NEUROPATHIES- 3 CASES

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The conventional dosing of IVIg in CIDP and MMN is based on treatment trials that used bolus and maintenance dosing of IVIg between 1-2.5g/kg. There are rare published articles reporting the efficacy of higher maintenance IVIg doses. We present three cases of inflammatory neuropathies, who are currently stabilized on IVIg doses of 2mg-8mg/kg of IVIg per month, refractory to standard dose IVIg and other immunosuppressants. The first case is a 35 year-old-lady with CIDP who presented with 3 episodes of ascending sensory disturbance, weakness, and diplopia. She had activity related fluctuations and pre-dose deterioration on 2g/kg/month IVIg. She then had an acute deterioration with MRC sum score dropping from 70 to 49 even with additional plasma exchange. Her bilateral foot drop (MRC Grade 2-3) and fluctuations persisted with an increase of IVIg to 4.6g/kg/month. She is now clinically stable (ankle dorsiflexion MRC Grade 4-5, MRC sum score 67) on mycophenolate and 80g IVIg weekly (5.3g/kg/month). Case 2 is a 45-year-old male fitness instructor with MMN and Sjogren's syndrome. He presented with recurrent proximal and distal weakness that responded to 2g/kg of IVIg and deteriorated with IV methylprednisolone. He had peri-dose fluctuations, intermitted proximal weakness, and persistent foot drop (ankle dorsiflexion MRC grade 2-3) at 2.83mg/kg/month, worsening to MRC grade 1-2 on 4.33g/kg/month and fluctuating between MRC grade 0-3 on 5.7g/kg/month. An increase of IVIg to 180g weekly (8.52g/kg/month), has resulted in MMN RODS scores of 50/50, improved distal power and return to full capacity at work. Case 3 is a 52-year-old man with predominantly upper limb CIDP. He received 2g/kg IVIg without any benefit, had no response to 2 doses of plasma exchange, 10 doses of cyclophosphamide or 1 dose of rituximab between 2010 and 2012. Since 2013, he has received 2g/kg/month IVIg with improvement of MRC sum score from 50 to 68. These cases highlight that some patients require a much higher than conventionally prescribed dose of IVIg, and that these doses are tolerated over years without serious adverse events.

REDUCED INTRAEPIDERMAL NERVE FIBER DENSITY IN PATIENTS WITH REM SLEEP BEHAVIOUR DISORDER

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Idiopathic rapid eye movement sleep behaviour disorder (iRBD) has been identified as a precursor of alpha-synucleinopathies, such as Parkinson's disease, dementia with Lewy bodies, multiple system atrophy. Several studies linked changes in cutaneous

innervation with central nervous system pathology in neurodegenerative disorders. Recently small fiber neuropathy and alpha-synuclein deposition in the skin found to be a potential biomarker in Parkinson's disease. We evaluated the epidermal innervation of 18 iRBD patients and 22 age and sex-matched controls from skin punch biopsies from the distal leg using PGP9.5 immunohistochemistry. Furthermore, a battery of clinical examinations were performed on patients and controls alike, including structured interviews, clinical motor and non-motor questionnaires and rating scales (e.g. Unified Parkinson's disease rating scale [UPDRS], non-motor symptoms questionnaire [NMS-Quest] and Beck depression inventory, Epworth Sleepiness Scale, evaluation of cognitive and olfactory functioning as well as blood samples. iRBD patients, compared to controls, showed a significant reduction in intraepidermal nerve fiber density (p = 0.037), whereas the axon swelling ratio, did not differ between groups. Patients with iRBD reported non-motor symptoms more frequently than controls (UPDRS I, NMS-Quest). Olfaction and daytime sleepiness differed between both groups, whereas there were no differences regarding cognition.
These *in vivo* findings demonstrate small fiber neuropathy in iRBD patients that are associated with non-motor symptoms indicating that peripheral abnormalities may occur early in iRBD. They warrant larger scale longitudinal studies in order to investigate their prognostic value.

FIRST GLOBAL MULTIFOCAL MOTOR NEUROPATHY (MMN) QUALITY OF LIFE (QOL) PATIENT SURVEY IDENTIFIES NEEDS IN EDUCATION AND TREATMENT

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Multifocal Motor Neuropathy (MMN) is a rare condition that affects 0.6 in every 100,000 individuals worldwide and is associated with motor dysfunction and moderate to severe disability. The Neuropathy Action Foundation conducted a global survey to determine the impact of MMN on patient Quality of Life (QOL) and gaps in patient/provider educational needs. The first global MMN QOL survey was an 87 item internet questionnaire available between January 21 and July 21, 2016. The survey focused on three primary areas : timely and accurate diagnosis, the efficacy of treatment, and the impact of the disease on patients QOL. The survey was completed by 214 patients from 24 countries. The majority of respondents said they were diagnosed between the ages of 41 and 65 years (56.52%), more than 67% reported that it took more than one year to be diagnosed and more than 44% reported that it took 2-3 years or longer to be accurately diagnosed. With respect to treatment options : 91.43% reported receiving intravenous immune globulin and 8.57% reported receiving subcutaneous immune globulin therapy. Other therapies being used to treat MMN were gabapentin (6.6%), and pregabalin (5%). Almost half (49.49%) said that MMN often impacts their overall schedule. Half of the participants reported that MMN often or always interferes with their employment; 46% had difficulty typing on a computer or using a telephone, 46.19% had trouble concentrating, and 38.07% said they had to work really hard to pay attention or else they would make a mistake. This is the first assessment of MMN from a patient's perspective. The survey highlighted critical issues relating to the diagnosis, management, and impact on the QOL of individuals with MMN. The data also identified gaps and insights in provider education relating to proper diagnoses and management of the condition from a patient's perspective.

IMPROVING REVIEW PROCESSES FOR IVIG THERAPY: GETTING TO KNOW OUR AUNTS (AUSPICOUSLY UNINTERPRETABLE NOTE TAKING) AND UNCLES (UNCERTAIN NEUROLOGICAL CLINICAL ENTITIES)

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In the United States, CIDP cases are submitted to insurance companies to determine whether IVIg therapy is appropriate. This is done using specified diagnostic criteria, which reduce diagnosis to a Boolean analysis, where a disease can only be present or absent. This leaves no room for uncertainty, even when it truly exists. Boolean criteria are useful for clinical trials, but fall short where real decisions are made under uncertainty and based on perceived cost/benefit analysis. This project attempts to elucidate root causes of uncertainty and to find solutions to this dilemma. We asked 8 CIDP experts to select a single diagnosis in 29 cases where IVIg was approved using the submitted case records. While there was agreement on many cases, in the five most "uncertain" cases no more than 4 reviewers agreed on a single condition, who chose up to four separate entities. Among these, at least three reviewers diagnosed an immune neuropathy in all five. The root cause of the disagreement, to a large degree was unclear documentation (AUNTs) which consisted of pasted, missing, and disorganized data. Reviewers missed useful information, admitting it was too difficult to fully parse records. To resolve uncertainty, reviewers admitted to discounting certain reported datum to help fit the entity they suspected, such as reported therapeutic responses or certain electrodiagnostic/exam findings. Other disagreement, however, reflected the complexity of neuropathy diagnosis, such as knowing if improvement was due to natural history or treatment, unawareness of rare presentations, or analyzing a true UNCLE (complex case). Reviewers used Bayesian (select most likely diagnoses from a list) and Fuzzy logic (compare best fits to base cases). When the "best" diagnosis did not fit the base case,

they had to re-interpret the data. Improving review procedures requires eliminating AUNTS by collecting all key information and simplifying how records are presented. It also needs more advanced data methods to analyze common and rare borderline presentations (UNCLES like MAMA v PMA, CIDP v CSPN, etc..), developing diagnostic algorithms that address real uncertainty, educating prescribers and patients on process, and creating systems that measure outcomes longitudinally after induction or tapering of therapy.

DIFFERENCES OF ANTIBODY REACTIVITIES AGAINST GLYCOLIPID COMPLEXES AMONG GUILLAIN-BARRÉ SYNDROME, MILLER FISHER SYNDROME AND BICKERSTAFF BRAINSTEM ENCEPHALITIS

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Anti-ganglioside antibodies are closely associated with clinical phenotype and specific symptoms in acute immune-mediated neuropathies. IgG anti-GQ1b antibodies are specifically associated with Miller Fisher syndrome (MFS), Bickerstaff brainstem encephalitis (BBE) and Guillain-Barré syndrome (GBS) with opthalmoplegia (GBS-OP). In addition, ganglioside complexes (GSCs) containing GQ1b also can be targets in such diseases, and might be associated with the clinical features. However, factors regulating clinical phenotype in those GQ1b-associated antibodies-positive diseases have not yet been known. For investigating the differences of antibody reactivities among those diseases, we examined, using combinatorial glycoarray, IgG antibodies to ten individual glycolipids [GM1, GM2, GM4, GD1a, GD1b, GQ1b, Galactocerebroside (Gal-C), Lactosylceramide (LacCer), GA1, Sulfatide] and 45 glycolipid complexes consisting of two of the glycolipids listed above in sera from 36 patients with GBS-OP who were positive for anti-GQ1b antibody by ELISA (GBS-OP-GQ1b), 40 patients with MFS with the clinical triad (opthalmoplegia, ataxia, and areflexia), and 27 patients with BBE. By combinatorial glycoarray, overall sensitivity of antibodies to GQ1b and GSCs containing GQ1b was 97.2% (35/36) in GBS-OP-GQ1b, 87.5% (35/40) in MFS, and 74.1% (20/27) in BBE, respectively. There were no significant differences in antibody reactivities between MFS and BBE. It is notable that antibodies to GSCs containing GD1b were more frequently found in GBS-OP-GQ1b patients than in MFS or BBE patients (e.g., GD1b/Sulfatide: $p=0.024$ and $p<0.01$, respectively). Presence of the antibody reactivities to GSCs containing GD1b may possibly be related with clinical features of GBS-OP-GQ1b, including frequent need of artificial ventilation.

GAIT IN CHILDREN AND ADOLESCENTS WITH CHARCOT-MARIE-TOOTH DISEASE: A CASE CONTROLLED STUDY OF GAIT IN DIFFERENT FOOTWEAR CONDITIONS

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Problems with walking and footwear fit are often reported by children and adolescents with Charcot-Marie-Tooth disease (CMT). A cross-sectional, case controlled study of gait was conducted in children with CMT and typically developing (TD) children. Gait was assessed barefoot and in two types of the participants' own typical footwear; optimal (e.g. athletic shoes) and suboptimal (e.g. slip-on footwear). The aims were to determine differences in spatio-temporal (S-T) gait variables between children with CMT and TD children; and to investigate the effect of footwear choices. Twenty-nine independently ambulant children aged 4-18 years with confirmed genetic or clinical diagnoses of CMT, and 29 age and gender matched TD children participated (mean age 11.5 years; 40 males). Exclusion criteria included developmental disorders, other neuromuscular conditions or musculo-skeletal diseases that could affect gait, and lower limb injury or surgery in the preceding 6 months. Assessment included S-T gait patterns, footwear characteristics, 10 metre run, and CMTPedS. Gait was assessed at self-selected speed with an electronic walkway (GAITRite™), with 6 trials for each condition. The primary gait variable assessed was speed; other variables included step length, step time, cadence, base of support width and step-to-step gait variability. Across all footwear conditions children with CMT walked more slowly (optimal CMT 1.26 [0.15] m/s, TD 1.40 [0.13] m/s; suboptimal CMT 1.18 [0.20] m/s, TD 1.31 [0.14] m/s; barefoot CMT 1.20 [0.16] m/s, TD 1.31 [0.13] m/s; all $p<0.05$) with shorter steps (optimal CMT 64.4 [8] cm, TD 69.9 [9] cm; suboptimal CMT 61.6 [11] cm, TD 66.3 [10] cm; barefoot CMT 59.0 [8] cm, TD 63.8 [10] cm; all $p<0.05$) and wider base of support (optimal CMT 9.9 [2.8] cm, TD 7.3 [2.5] cm; suboptimal CMT 10.3 [3.0] cm, TD 7.5 [2.5] cm; barefoot CMT 9.2 [2.9] cm, TD 7.1 [2.5] cm; all $p<0.05$) . Gait performance in optimal footwear for both groups was significantly faster compared to suboptimal and barefoot. Children with CMT had significantly greater step-to-step variability in base of support width in all footwear conditions. Children with CMT walk slower than TD children with shorter, wider steps and increased variability. Footwear type affects gait.

LONG-TERM OUTCOME OF INTRAEPIDERMAL NERVE FIBER REGERNATION IS IMPAIRED IN DIABETIC PATIENTS, BUT IS INDEPENDET OF AXON LENGTH OR BLOOD GLUCOSE LEVEL.

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Regeneration of cutaneous unmyelinated axons is known to be slowed in DM-patients and after 3-months, the density of intraepidermal nerve fibers

(IENF) does not return to baseline levels after chemical or mechanical axotomy. However, the long-term outcome of regeneration in DM or control subjects is not known. Additionally, it is not clear if the regeneration of sensory distal axons is length-dependent. Here we measured the rate of axonal regeneration 6-months after chemical denervation using a capsaicin model in DM patients (n=11/37 DM1/DM2) without neuropathy, and 5 controls. DM skin punches were performed at distal thigh at baseline, 48-hours post-capsaicin, and at 28, 90, 150 and 180 days. Blood glucose and HgbA1C were measured at baseline, 90, 150 and 180 days. Healthy controls had skin punches at both distal leg and proximal thigh at baseline, after capsaicin chemical axotomy, and days 28, 60, 90 and 180. Regeneration rate was significantly higher at the thigh in healthy controls (0.1 fibers/mm/day (95% CI: 0.04–0.18 fibers/mm/day) compared to DM (p=0.043), but no difference between DM1 (0.07 fibers/mm/day 95% CI: 0.01–0.13 fibers/mm/day) or DM2 (0.06 fibers/mm/day 95% CI: 0.01–0.12 fibers/mm/day) (p=0.4). Comparing regeneration rate at different time intervals, showed that regeneration was significantly slowed between day 150 and 180 DM patients, while it continued with the same rate in controls. Blood glucose or HgA1C had no effect on regeneration rate. IENFD returned to baseline in controls by 6-months (118% of baseline) while it is did not in DM subjects, 76%/58% (DM1/DM2) of IENFD baseline, (p=0.003 DM vs. controls). There was no difference in regeneration rate IENFD %-baseline by 6-months at distal leg and proximal thigh in controls (p=0.61). These results suggest that the rate and outcome of regeneration is independent of the length of the axon. Additionally diabetic patient have incomplete nerve regeneration after 6 months regardless of diabetes type or the level of glycemic control. Regeneration of axons slowed down over time in patients with DM and reached a plateau after 150 days.

SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF THE FCRN INHIBITOR UCB7665: A PHASE I STUDY

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UCB7665 is a humanised high-affinity monoclonal IgG antibody developed to bind human neonatal Fc receptor (FcRn), selectively inhibiting IgG salvage and recycling. Conditions such as myasthenia gravis (MG) are characterised by pathogenic IgG autoantibodies; inhibition of FcRn may provide a suitable therapeutic approach.[1] This Phase I, double-blind, dose-escalating, first-in-human study (NCT02220153) evaluated the safety and pharmacology of UCB7665. Forty-nine healthy adults (mean age 44 years, range 22–65) were randomised and received a single dose of intravenous (IV) or subcutaneous (SC) placebo (n=7 and n=6, respectively), or a single dose of IV or SC UCB7665 (1, 4 or 7 mg/kg; n=6 per dose, per administration). Subjects were followed up until Day 85. One placebo IV subject did not complete the study. Twenty-seven of 36 subjects (75%) receiving UCB7665, and 9/13 (69%) receiving placebo, reported ≥1 treatment-emergent adverse event (TEAE) of mild/moderate intensity. Severe TEAEs occurred in four subjects, all in the UCB7665 7 mg/kg IV group (headache [n=3], back pain [n=1]). No serious AEs occurred. Incidence of infections was similar with UCB7665 and placebo. The most frequently reported infection was nasopharyngitis. Treatment-related TEAEs were reported by 67% of subjects receiving UCB7665 and 54% receiving placebo: the most common in the UCB7665-treated groups were headache (14/36; 39%) and vomiting (9/36; 25%); these occurred more frequently with the IV than SC route. Non-linear increases in UCB7665 plasma concentration–time profile with increasing dose were observed with UCB7665. Serum IgG was reduced in a dose-depended manner with UCB7665 IV and SC: decreases from baseline to Day 10 with UCB7665 IV were 14.5%, 33.4% and 47.6% for 1, 4 and 7 mg/kg doses, respectively, and 16.8%, 25.9% and 43.4%, with UCB7665 SC doses, respectively. These data indicated that the FcRn inhibitor UCB7665 effectively reduced serum IgG, with SC administration generally better tolerated than IV. Further to these observations, the efficacy, safety and tolerability of UCB7665 SC for chronic–intermittent treatment of moderate-to-severe MG are being evaluated in an ongoing Phase II, multi-centre, randomised, double-blind, placebo-controlled study (EudraCT 2016-002698-36).

[1]Roopenian and Akilesh. *Nat Rev Immunol* 2007;**7**:715–25

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NEUROLOGICAL COMPLICATIONS IN MIDDLE EAST RESPIRATORY SYNDROME

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Middle East respiratory syndrome (MERS) has a high mortality rate and pandemic potential. However, very little information has become available on this syndrome since it first erupted in 2012. This study aimed to evaluate the frequency of neurological complications and their clinical presentations in MERS. We reviewed the medical records of all patients who were diagnosed with laboratory-

confirmed MERS coronavirus (CoV) infections and subsequently admitted to a single reference center for MERS treatment during the 2015 outbreak in Korea. In total, 4 patients (17.4%) reported neurological symptoms during or after MERS-CoV infection. The potential diagnoses in these 4 cases included Bickerstaff's encephalitis overlapping with Guillain-Barré syndrome, critical illness polyneuropathy or other toxic or infectious neuropathies. Neurological complications did not appear concomitantly with respiratory symptoms, but were instead delayed by 2-3 weeks. Neuromuscular complications were not rare in MERS-CoV-infected patients, and they may have previously been underdiagnosed. Understanding neurological manifestations is important in an infectious disease like MERS, because evaluation is frequently limited during treatment, but it can interfere with prognosis and sometimes require modification of treatment.

USEFULNESS OF VARIOUS ULTRASONOGRAPHIC FINDINGS IN CARPAL TUNNEL SYNDROME

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The diagnosis of carpal tunnel syndrome (CTS) is based on clinical symptoms, physical examinations and supported by nerve conduction study (NCS). Ultrasonographic examinations can be performed to assess peripheral nerves with less discomfort and the surrounding anatomic structures. While the usefulness of ultrasonography (USG) in the CTS has been reported, no study to date has compared the diagnostic utility of various USG findings for CTS. We investigated the correlation of various USG findings to the clinical symptoms/signs and NCS findings in patients with CTS. Twenty-eight hands (17 patients) with CTS based on electrodiagnostic criteria and clinical symptoms such as tingling sensation or pain in the first to third fingers, burning sensation, paresthesia and weakness of hand grip power. All subjects were examined with USG. Cross-sectional area (CSA) and flattening ratio (FR) of the median nerve was calculated at level of radio-ulnar joint, pisiform and hamate. Swelling ratio of the median nerve and palmar displacement of the flexor retinaculum was also calculated. Clinical assessment was conducted using the Boston carpal tunnel questionnaire (BCTQ) scale and Historical-Objective (Hi-Ob) scale. The analysis of correlation between USG findings and clinical symptom scales/NCS findings was performed using correlation analysis. The CSA of the median nerve at level of radio-ulnar joint was significant correlated with BCTQ scale, Hi-Ob scale, distal motor latency, and conduction velocity (CV). The CSA of the median nerve at level of pisiform was significantly correlated with Hi-Ob scale, distal motor latency, and CV. The FR of the median nerve at level of radio-ulnar joint was significantly correlated with BCTQ scale, Hi-Ob scale, distal motor latency, and CV. The swelling ratio of the median nerve was also significantly correlated with distal motor latency and CV. In patients with CTS, CSA of the median nerve at level of radio-ulnar joint was most closely related to NCS findings and clinical symptoms. So, CSA of the median nerve at radio-ulnar joint might be a complementary tool for the diagnosis of CTS.

SONOGRAPHIC NERVE ENLARGEMENT IN SARCOID PERIPHERAL NEUROPATHY - A CASE REPORT

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The case was a 73-year-old woman. First, she noticed paresthesia in the right plantar eight months before admission and in the left plantar four months before admission. Three months before admission, she developed muscle weakness in her feet. The muscle weakness and paresthesia extended to the lower legs in a few months. Twenty days before admission, she experience difficulty in walking. On admission, the muscle weakness was observed in the legs, especially in the right tibial anterior muscle (TA). There was severe sensory disturbance and loss of deep tendon reflex in the legs. She had trouble walking due to the weakness and sensory aphasia. In nerve conduction study (NCS), conduction block was observed between the ankle and popliteal in both tibial nerves. The blood level of angiotensin converting enzyme (ACE) was elevated. Cerebrospinal fluid analysis was normal. There was no enhancement in the lumbar nerve roots shown on MRI. Gallium-67 scintigraphy showed hot spots on bilateral hilar lymph nodes and mediastinal nodes and biopsy of mediastinal nodes showed non-caseating epithelioid granuloma. Therefore, we diagnosed her with sarcoid peripheral neuropathy by sarcoidosis. By using the nerve ultrasound, partial spindle-shaped nerve enlargement was observed at the part of conduction block in the left tibial nerve. We started the treatment with methyl prednisolone (1000mg, 3days) and oral prednisolone therapy (1mg/kg/day). After treatment, the paresthesia and muscle weakness in the legs had gradually improved. The partial enlargement in the left tibial nerve also improved on the 52-hospital day. In NCS, the conduction block improved, however, the compound muscle nerve potential of tibial nerve decreased because of axonal damage. This partial spindle-shaped nerve enlargement by using ultrasound has never been reported in sarcoid peripheral neuropathy before. The nerve ultrasound may be useful for evaluation of therapeutic effect of sarcoid peripheral neuropathy.

THE EFFECT OF CURCUMIN ON PERIPHERAL NERVE REGENERATION

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Peripheral nerve injuries are still debating problems in the world because of poor recovery. There is absolutely a need for new therapeutic agents to improve outcome by altering nerve regeneration. There are some studies in the literature about some therapeutic agents that used in the cases of peripheral nerve injuries. Despite these studies, an agent with clinical use has not been presented yet. In this experimental study, we aimed to analyze the effects of curcumin (CUR) in the cases of peripheral nerve injuries. Forty rats were randomly and equally divided into four groups. The first group was control group. Rats in this group were not operated. Right sciatic nerve injuries were performed to the other groups. The second group was operation group with no therapeutic agent. The third group was operation and local CUR applied group. The fourth group was operation and systemic CUR applied group. Electrophysiological evaluations were performed with electroneurography (ENoG) before and after the surgeries. Systemic use of CUR although caused improvement in the ENoG values but could not make a positive contribution to the nerve regeneration statistically. Additionally local use of CUR made negative effect to the nerve regeneration statistically. According to our statistical results we could not recommend CUR as a nerve protective agent.

GENOMIC ANALYSIS REVEALS FREQUENT *TRAF7* MUTATIONS IN INTRANEURAL PERINEURIOMAS

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Intraneural perineurioma is a hypertrophic peripheral nerve tumor having immunoreactivity to epithelial membrane-antigen, negative for S-100. The origin of perineurial cells is debated to be similar to meningeal cells. IP does not metastasize, but motor deficits accumulate over time from tumor growth in nerve and plexus. After schwannomas and neurofibromas, perineuriomas are the most common nerve tumor of young adults. A chromosome 22q deletion has been reported in one patient. We identified16 IP cases from our previously published clinical cohort with available flash frozen IP tissue for DNA isolation. WES with CNV analysis and CGH microarray analysis (Agilent 2x400K SuperPrintG3) were performed on extracted DNA; 7 had available germline DNA (lymphocytes and buccal tissue). We compared the exome data against online and in-house control data (~100,000) examining variants less than 0.0001 frequencies, predicted damaging or nonsynonymous. WES identified three novel, heterozygous, damaging mutations in Tumor Necrosis Factor Receptor-Associated Factor 7 (TRAF7) in 10 of 16 (60%) cases; p.L519P (n=3), p.H521R (n=3) and p.S561R (n=4). Mutations were within the WD40 domain, p.L519P, p.H521R within exon 17 and p.S561R within exon 18, and mapped to a limited region of TRAF7 with protein structure modeling. Two of 16 cases (12.5%) showed macroduplications/deletions on multiple chromosomes, including chromosome 22, confirmed with CGH microarray analysis and CNV results from exome data analysis. Four of 16 (25%) had no discovered mutation. Age of onset or severity did not correlate with type of mutations. This study provides strong evidence that TRAF7 is a specific tumor driver of IP. Mutations in TRAF7 are also linked to benign intracranial meningiomas suggesting a shared pathogenesis and close origins of perineurial and meningeal cells.

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NEUROTOXICITY OF PACLITAXEL: IMPACT OF NANOPARTICLE - AND SOLVENT - BASED FORMULATION

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Peripheral neuropathy is a common side effect of paclitaxel. Clinical evidence suggests that the delivery mechanism of paclitaxel formulations influence time course and severity of paclitaxel induced peripheral neuropathy. In a preclinical model we studied access, distribution and toxicity of two paclitaxel formulations (nanoparticle albumin-bound paclitaxel (nab) and solvent-based paclitaxel) in the peripheral nervous system (PNS). C57BL/6 mice were treated with 5 mg/kg or 10 mg/kg of nab-paclitaxel or solvent based paclitaxel. Kinetics of paclitaxel in neurons was assessed by a newly established immunostaining technique. Neurotoxicity was evaluated by functional assays and nerve morphology. Paclitaxel accumulated mostly in dorsal root ganglia, whereas distal nerve segments showed only low uptake of paclitaxel. Treatment of mice with the two paclitaxel formulations resulted in paclitaxel uptake mostly in NF200+ larger fiber neurons. In IB4+, and CGRP+ small fiber neurons, paclitaxel was less frequently detected. Nab-paclitaxel was incorporated more rapidly compared to solvent-based paclitaxel but neurons also showed a faster clearance of nab-paclitaxel compared to solvent based paclitaxel. Functional assays and nerve conduction studies indicated that nab-paclitaxel was less neurotoxic compared to solvent-based paclitaxel. This is the first study that characterizes in detail the access of nab-paclitaxel and solvent based paclitaxel into the PNS. Our findings have important implications to understand the pathomechanisms of paclitaxel induced neurotoxicity and to develop neuroprotective strategies by preventing access of paclitaxel to the PNS.

NEUROPATHY IN RHEUMATOID ARTHRITIS: VASCULITIC OR IMMUNE-MEDIATED NEUROPATHY

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The aim of our study was to investigate the etiology of neuropathy in patients with rheumatoid arthritis

(RA). Subjects were 9 neuropathy patients with RA admitted to our department. Laboratory investigations, nerve conduction studies (NCS) and sural nerve biopsy were performed. Mean patient age was 66.1 years (range, 41-84 years), and mean disease duration was 10.5 years (range, 2-24 years). Clinical diagnosis for neuropathy was rheumatoid vasculitis (RV) in 5 patients, RV with acute motor axonal neuropathy (RV-AMAN) in 1 and chronic inflammatory demyelinating polyneuropathy with RA (RA-CIDP) in 3. Rheumatoid factor (4/5) and rheumatoid arthritis particle agglutination (3/3) was high and C4 tended to be lower in the RV group (RV and RV-AMAN). Anti-ganglioside antibodies were examined in 4 patients, with positive results in 2. An RV-AMAN case was diagnosed with motor-dominant clinical presentation and the presence of anti-GalNac-GD1a immunoglobulin (Ig)G antibody. No other cases with RV were examined for anti-ganglioside antibodies. Positive results for anti-GM1 and GM2 IgG antibody were seen in one RA-CIDP patient. We evaluated sural/median (S/M) ratio) for sensory nerve action potential (SNAP). S/M ratio was low in RV cases (4/5) and high (3/3) in immune-mediated cases, suggesting a so-called normal sural abnormal median pattern in immune-mediated neuropathies. The RV-AMAN case showed a moderate value in S/M ratio. Nerve biopsy revealed thinly myelinated nerve fibers in RA-CIDP cases compatible with demyelination, while the RV group showed the typical pathology for necrotizing vasculitis. RV cases were treated with prednisolone (PSL), intravenous methylprednisolone, intravenous cyclophosphamide and increased PSL dose. RA-CIDP and RV-AMAN were treated with intravenous Ig. In conclusion, neuropathy in RA can be divided into vasculitic and immune-mediated groups. NCS, and the S/M ratio of SNAP with some laboratory parameters in particular, may be of use in differential diagnosis and deciding treatment strategies.

TREATMENT INDUCED NEUROPATHY OF DIABETES MELLITUS IS UNCOMMON IN A GENERAL DIABETES MELLITUS COHORT

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Treatment-induced neuropathy of diabetes mellitus (DM) (TIND) is an acute painful autonomic neuropathy that develops with abrupt improvement in glycaemic control. Typically, Type 1 or 2 DM patients on insulin or oral hypoglycaemic agents (OHGA), present with painful neuropathy and autonomic dysfunction within 8 weeks of rapid improvement in glucose control. Current emphasis to achieve good glycaemic control rapidly may inadvertently increase incidence of TIND, hence the impetus to understand risk of over-zealous glycaemic control. We therefore set out to study the occurrence of TIND in a DM cohort of a tertiary hospital. We screened all patients who had two HbA1c measurements between 2014 and 2015. During this period, approximately 5000 patients were seen per year. We found 1562 patient-encounters that showed HbA1c decrease of ≥2% over 3 months or ≥4% over 6 months. We then used a structured checklist of TIND symptoms to shortlist 62 cases. These case-encounters were scrutinised and classified as; 'Probable TIND': acute painful neuropathy AND acute dysautonomia WITH temporal relationship to the decrease in HbA1c; 'Possible TIND': acute painful neuropathy OR acute dysautonomia OR uncertain temporal relationship to decrease in HbA1c; Unlikely TIND: alternative explanation exists for symptoms. Only one case was deemed 'Probable TIND'- a middle-aged man with newly diagnosed type 2 DM who presented to emergency department with palpitations and worsening 'frozen feet' sensation that disturbed sleep. His HbA1c decreased by 2.3% in 2 weeks. His symptoms improved within a month with neuropathic pain medications and resolved 4 months later. He also developed maculopathy and proliferative retinopathy. Ten months later, he developed significant proteinuria. Four other cases were classified as 'Possible TIND' while the remaining 57 were unlikely TIND. Our study is limited by retrospective design and reliance on hospital records. Nevertheless, our findings suggest that TIND is uncommon in a general cohort of DM patients. On the other hand, the number of patients with painful neuropathy and acute dysautonomia symptoms contemporaneous with rapid decline in HbA1c raises the intriguing possibility that forme fruste of TIND exists and one should interrogate the rate of HbA1c decline in DM patients with these symptoms.

PARANODAL DISSECTION IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY WITH ANTI-NEUROFASCIN 155 AND ANTI-CONTACTIN 1 ANTIBODIES

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We investigated the morphological features of chronic inflammatory demyelinating polyneuropathy (CIDP) with autoantibodies directed against paranodal junctional molecules, particularly focusing on the fine structures of the paranodes. Sural nerve biopsy specimens obtained from 9 CIDP patients with anti-neurofascin 155 antibodies and 1 patient with anti-contactin 1 antibodies were assessed. These antibodies were examined using sera obtained from 131 patients with CIDP who fulfilled the criteria of the European Federation of Neurological Societies/Peripheral Nerve Society. Thirteen CIDP

patients without these antibodies were also examined to compare pathological findings. Characteristic light and electron microscopy findings in transverse sections from patients with anti-neurofascin 155 and anti-contactin 1 antibodies indicated a slight reduction in myelinated fiber density, with scattered myelin ovoids, and the absence of macrophage-mediated demyelination or onion bulbs. Teased-fiber preparations revealed that segmental demyelination tended to be found in patients with relatively high frequencies of axonal degeneration and was tandemly found at consecutive nodes of Ranvier in a single fiber. Assessment of longitudinal sections by electron microscopy revealed that detachment of terminal myelin loops from the axolemma was frequently found at the paranode in both anti-neurofascin 155 and anti-contactin 1 antibody-positive CIDP patients compared with antibody-negative CIDP patients. Patients with anti-neurofascin 155 antibodies showed a positive correlation between the frequencies of axo-glial detachment at the paranode and axonal degeneration, as assessed by teased-fiber preparations ($p < 0.05$). In conclusion, paranodal dissection without classical macrophage-mediated demyelination is the characteristic feature of patients with CIDP with autoantibodies to paranodal axo-glial junctional molecules.

SCHWANN CELL AND ENDOTHELIAL CELL DAMAGE IN TRANSTHYRETIN FAMILIAL AMYLOID POLYNEUROPATHY

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Peripheral neuropathy is the cardinal feature of familial amyloid polyneuropathy (FAP), but its mechanism has not been fully elucidated. We used electron microscopy to examine Schwann cells and endoneurial microvessels. Sural nerve biopsy specimens from 49 FAP patients with transthyretin Val30Met mutation were assessed. Patients were consisted of 11 early onset cases from endemic foci and 38 late onset cases from non-endemic areas. Loss of nerve fibers with or without neighboring amyloid deposition was a common feature. The amount of amyloid deposition was greater relative to the extent of nerve fiber loss in early onset cases than in late onset cases. The atrophy of Schwann cells, particularly nonmyelinating cells, that were apposed to amyloid fibrils was more conspicuous in early onset cases than in late onset cases. The numbers of endothelial cell nuclei, endothelial cell profiles, and occluded microvessels were significantly increased in the FAP patients compared with 37 patients with nutritional/alcoholic neuropathies ($p < 0.05$, 0.01, and 0.01, respectively). Findings suggestive of the disruption of blood-nerve barriers, such as the loss of tight junctions and the fenestration of endothelial cells, were also more frequently found in the FAP patients ($p < 0.001$), irrespective of the presence or absence of amyloid deposition. In conclusion, these findings suggest that direct insult of amyloid fibrils causes Schwann cell damage resulting in the predominant loss of small-fiber axons characteristic of early onset cases. In addition, vasculopathy may also participate in the pathogenesis of neuropathy, particularly in late onset cases.

A RANDOMIZED TRIAL OF AN AUTOMATED CIPN SYMPTOM MANAGEMENT SYSTEM

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Chemotherapy induced peripheral neuropathy (CIPN) is a major cause of morbidity due to numbness, pain, and gait instability. This prospective study compares the current standard care for CIPN symptom management to a new care delivery model which utilizes an automated symptom tracking program paired with a nurse practitioner led intervention triggered by moderate to severe symptoms. All participants beginning taxane or platin based chemotherapy called a telephone based automated symptom tracking program daily (Symptom Care at Home - SCH) to report chemotherapy related numbness and tingling. SCH tracked the presence and severity of neuropathic symptoms and their interference with activities of daily living (ADLs) on a 0-10 scale. Participants were randomized to two groups. The usual care (UC) group was advised to call their oncology provider for recommendations on symptom management. In the nurse practitioner (NP) group, when symptom severity was ≥ 4 participants received automated self care strategies and a call from a nurse practitioner to provide treatment recommendations based on consensus guidelines. 252 patients participated in the study. Mean duration of follow up was 90.2 ± 39.9 days with 81.1 ± 40.3 calls. The NP group had fewer days with any neuropathic symptom (12.7% ± 18.3 vs. 21.1% ± 26.1, p=0.005), with moderate to severe neuropathic symptoms **(**7.5% ± 12.4 vs. 15.4% ± 22.8, p< 0.001) or days of distress from neuropathic symptoms (12.7% ± 18.3 vs. 21.1% ± 26.1, p=0.005). On days with moderate to severe symptoms participants also reported burning (20.4 ± 30.3 %), weakness (18.4 ± 27.2%), balance problems, (17.9 ± 28.1%), and tripping (16.7 ± 28.3%). There was no significant difference between groups in the interference in ADLs (NP 3.3 ± 1.9 vs. UC 3.8 ± 2.1, p=0.08). Overall the automated telephone system effectively identified neuropathy symptoms and their severity. Compared to usual care in which patients must independently reach out to their care team for symptom management, SCH is effective in decreasing symptom prevalence, severity and distress.

ANTIBODIES AGAINST THE NODE OF RANVIER, A FLOW CYTOMETRY ANALYSIS.

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Antibodies against proteins of the Node of Ranvier have been recently described in severe chronic inflammatory demyelinating polyradiculoneuropathies (CIDP). They target paranodal proteins, namely contactin (CNTN1) and neurofascin 155 (NF155). Cell-based assay and ELISA are available in research, but no gold standard technic is admitted for the detection in routine of these antibodies.
Our objective was to evaluate if flow cytometry analysis is an efficient technic to detect antibodies against CTN1 and NF155 in a large cohort of CIDP patients.
Flow cytometry analysis were performed on a BD FACS-Diva. Human Embryonic Kidney (HEK) cells were transfected either with NF155 or CNTN1. Sera were diluted 1/100. Antibodies anti-CNTN1 or NF155 were revealed using FITC conjugated anti human IgG antibodies. Delta MFI (mean fluorescence intensity) was calculated as MFI of transfected cells less MFI of non-transfected cells. Measures were normalized using positive controls and 60 negative controls from healthy blood donors.
156 sera of CIDP patients from different French neuromuscular referral centres were analysed with flow cytometry. Respective delta MFI were 25 (standard deviation 22) and 34 (standard deviation 29) for antibodies against NF155 and CNTN1 in CIDP antibodies negative patients.
Antibodies against NF155 were found in 3 patients (respective MFI 2036, 79, 15591) and against CNTN1 in two other patients (respective MFI 4693 and 708). Isotype of these antibodies was IgG4 in 3 patients and IgG4 and IgG3 in the remaining patient. All the patient had severe CIDP. Four patients had poor response to intravenous immunoglobulins (IVIg) and have been treated with immunosuppressive drugs. As usually reported, the patient with anti-NF155 antibodies had postural tremor.
Flow cytometry seems effective to detect antibodies against NF155 and CNTN1. Compared to other assays, benefits of flow cytometry are: to analyse a large number of sera in the same time and to give objective numerical results expressed in MFI that can be compared to the results of other samples. Further studies are needed to confirm that flow cytometry can be the best test to assess antibodies against CNTN1 and NF155 in routine.

INFLUENCE OF IVIG ON NERVE EXCITABILITY IN MULTIFOCAL MOTOR NEUROPATHY

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The mechanism by which intravenous immunoglobulins (IVIg) improves peripheral nerve function in multifocal motor neuropathy (MMN) is unknown. The rapid clinical improvement following IVIg could be related to blocking complement deposition on GM1 epitopes, change in ion-channel properties of affected motor axons, or both. The present study investigated median nerve motor excitability parameters at 37°C just before IVIg administration as well as at the peak of clinical improvement in 17 patients with MMN. The investigated nerves were characterized either by conduction block (n= 5), demyelinative slowing without block (n= 3), or motor axon loss (n=9). The results of motor excitability testing in MMN showed no difference between pre- and post IVIg recordings. Clinical assessment of APB muscle showed increase in MRC score in 6 patients and decrease in 1 patient after IVIg administration. In 10 patients MRC score of the APB remained the same. Those findings indicate that clinical changes following IVIg administration are not related to excitability parameters of affected motor axons in MMN.

SENSORY AXON EXCITABILITY IN MULTIFOCAL MOTOR NEUROPATHY

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Nerve conduction studies (NCS) in multifocal motor neuropathy (MMN) show localized segments in mixed nerves where impulse conduction is blocked or markedly slowed in motor axons but is normal in sensory axons. Sensory symptoms or signs are usually absent but have occasionally been reported in skin areas innervated by nerves with prominent motor axon loss. Although the mechanism of selective motor involvement in MMN is unresolved, it may be related to differences in antigenic properties between motor and sensory axons or differences in biophysical properties. The objective of the present study was to compare ion-channel activity in both motor and sensory axons of nerves affected by MMN. Affected nerves had to have motor conduction block, demyelinative slowing on motor NCS, or motor axon loss, whereas sensory NCS had to be normal. We performed excitability tests of motor and sensory axons in affected median nerves of 20 MMN patients and 20 healthy controls at 37°C. Conditioning and test stimuli were delivered at the median nerve at the wrist; CMAPs were recorded from the thenar muscle and SNAPs from the 3rd digit. Results of motor

excitability testing in MMN showed fanning-out of threshold electrotonus, decreased I/V slope, and increased superexcitability, all compatible with persistent hyperpolarization of resting membrane potential in motor axons. Sensory excitability testing in MMN showed decreased subexcitability but was otherwise normal. This may indicate minimal involvement of sensory axons in MMN.

MOTOR AXON EXCITABILITY IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1B WITH A NULL MUTATION IN THE P0 GENE – INSIGHTS FORM A MOUSE MODEL.

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Mutations in the gene coding for myelin protein zero (MPZ, P_0) are associated with different forms of Charcot-Marie-Tooth (CMT) disease. We describe a family harboring a frameshift mutation (c.306delA / p.Asp104ThrfsTer14) in the P_0 gene, predicted to result in a nonfunctional P_0 truncated very early in the extracellular domain. This offered the rare opportunity to assess the consequences P_0 deficiency in absence of the potential gain-of-function effects of the mutations itself. Conventional conduction studies and multiple measures of nerve excitability by "threshold tracking" were carried out in 2 heterozygote parents (aged 63 and 52) and their two homozygote sons (aged 31 and 39). In the homozygous patients, all distal limb CMAPs and SNAPs were absent. For neurophysiological assessment, the spinal accessory nerve was stimulated at the neck and CMAP was recorded over the upper trapezius muscle. Eight normal subjects, mean age 34, were used as control. The two sibs showed a severe phenotype with early onset, severe scoliosis, complete loss of distal movements and relevant proximal weakness, CMT Examination Score (CMTES) 23-25/28; both heterozygous parents had very mild adult-onset neuropathy with CMTES <4/28. Control subjects had a trapezius CMAP with a latency of 6.2 ms and an amplitude of 7.4 mV. Heterozygotes had a mild CMT type 1B phenotype, with a CMAP latency of 7.5 ms and an amplitude of 2.9 mV whereas the homozygotes had a severe neuropathy with a CMAP latency of 35.9 ms and an amplitude of 0.2 mV. Consistently, the homozygotes had a more severe impairment in excitability with a rheobase of 16.2 mA as compared to 4.7 mA in the heterozygote and 3.5 mA in controls. Deviations in excitability measures were similar to our previous reports in P_0+/- and P_0-/- mice. Mathematical modeling, indicated both altered passive cable properties due to dysmyelination and depolarizing features with increased Na+ currents. Our data suggest that P_0 deficiency is associated with impaired axonal Na+ channel function, arguing for the translational value of Na+ channel blocker treatments as found in P_0 null mouse models.

THE BURDEN AND JOURNEY OF PATIENTS WITH CIDP: A CASE-CONTROL ANALYSIS

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare neurological disorder of the peripheral nervous system. The objectives of this retrospective real-world study were to compare demographic and clinical characteristics among CIDP cases and matched controls and to assess CIDP treatment utilization. Adults newly diagnosed with CIDP between 7/1/2010 and 6/30/2014 were identified in the QuintilesIMS PharMetrics Plus Health Plan Claims Database (first diagnosis date termed the index date). Eligibility requirements were: confirmation of CIDP (second CIDP diagnosis or initiation of CIDP therapy) within 1 year of initial diagnosis, continuous health plan enrollment in the 6 months prior to diagnosis (the pre-index) and the 2 years following diagnosis (the follow-up), and no CIDP diagnosis or use of CIDP therapy in the pre-index. A total of 1,041 CIDP cases met the study eligibility criteria. Cases were direct-matched to controls based on age, gender, region, health plan, and payer type at index, and pre-index Charlson Comorbidity Index score. The final sample consisted of 790 cases matched to 790 controls (both: mean [SD] age 49.7 [11.4]; 53.7% male; 63.9% commercially-insured). Alternative pre-index diagnoses among cases included inherited neuropathies (38.9%) and chronic acquired polyneuropathies (17.6%). In the pre-index, neuropathic pain (39.7% vs. 2.9%), back pain (30.5% vs. 10.1%), and use of opioids (33.4% vs. 16.2%) and anti-convulsants (30.6% vs. 5.1%) were significantly higher among cases compared to controls ($p<0.0001$ for all). Median total pre-index healthcare costs were 2.2x higher for cases than controls ($4,751 vs. $2,209, $p<0.0001$). Over the follow-up, median total healthcare costs were 8.2x higher for cases than controls ($47,827 vs. $5,823, $p<0.0001$ [mean $116,330 and $15,586]). CIDP-related therapy costs accounted for 51.4% of total healthcare costs for cases. The majority of cases (83.2%) initiated CIDP therapy over the follow-up, in a mean of 115.5 (146.3) days from initial diagnosis. Half (48.7%) of cases initiated treatment with corticosteroids only, while 24.8% initiated IVIg only. Over the follow-up, 69.1% of cases used any corticosteroid, while 34.3% used any IVIg. Our findings suggest a substantial clinical and economic burden of CIDP compared to matched controls. Corticosteroids and IVIg were most commonly used to treat CIDP.

LARGE COVERAGE MR NEUROGRAPHY IN CIDP – DIAGNOSTIC ACCURACY AND ELECTROPHYSIOLOGICAL CORRELATION

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Objective: To evaluate large coverage magnetic resonance neurography (MRN) in chronic inflammatory demyelinating polyneuropathy (CIDP).
Methods: In this prospective study 18 patients with CIDP and 18 healthy controls were examined by a standardized MRN protocol at 3 Tesla. Lumbosacral plexus was imaged by a T2-weighted 3D-sequence (1 mm isotropic voxel size); peripheral nerves of the upper and lower extremity by axial T2-weighted turbo-spin-echo sequences (0.5 x 0.3 mm in-plane resolution). Lesions were characterized by nerve cross sectional area (CSA) and T2-weighted signal (nT2). Additionally, T2-relaxometry of the sciatic nerve was performed using a multi-spin-echo sequence. All patients received a complementary electrophysiological exam.
Results: Patients with CIDP exhibited increased nerve CSA and nT2 compared to controls ($p < 0.05$) in a proximally predominating pattern. ROC analysis revealed best diagnostic accuracy for CSA of the lumbosacral plexus (AUC = 0.88) and nT2 of the sciatic nerve (AUC = 0.88). CSA correlated with multiple electrophysiological parameters of demyelinating neuropathy (f-wave latency, nerve conduction velocity) of sciatic and median nerve, while nT2 only correlated with f-wave latency of sciatic and not median nerve. T2-relaxometry indicated that MR-signal increase in CIDP was due to increase in proton-spin-density ($p < 0.05$), and not increase in T2-relaxation time.
Conclusion: Both nT2 and CSA might aid in diagnosis of CIDP, but CSA correlates more robustly with electrophysiological parameters. Since best diagnostic accuracy was shown for proximal nerve locations, MRN may be a useful complementary tool in select CIDP cases.

PHYSIOLOGICAL CHARACTERIZATION OF NOCICEPTORS INNERVATING THE PLANTAR SKIN FOLLOWING NEUROPATHIC INJURY

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Damage of peripheral sensory nerves due to diabetes, *Herpes zoster* infection, chemotherapy or trauma can cause chronic neuropathic pain. Common symptoms include increased pain sensation (hyperalgesia), touch-induced pain (allodynia), paresthesia and spontaneous pain. We currently have poor understanding about the underlying molecular mechanisms at the peripheral level and treatment of patients suffering from neuropathic pain is inadequate. Recent meta-analysis studies show that common first-line medications only yield NNTs (numbers needed to treat) between 10.6 to 6.4. It is still unclear to what extent allodynia can be attributed to changes in the physiological properties of intact sensory afferents. In this study, we aimed to elucidate whether changes occur in intact sensory afferents that innervate the plantar skin of the hind-paw following induction of neuropathic symptoms. This question was of particular interest considering that blocking mechanotransduction in the skin can alleviate mechanical hypersensitivity in neuropathic pain models (Wetzel et al 2016 Nature Neuroscience 20(2):209-218). We used the chronic constriction injury (CCI) model in mice which is behaviourally characterized by robust mechanical hypersensitivity. We made electrophysiological recordings from primary afferent neurons which had intact axons passing through the constriction to innervate the plantar skin using an *ex-vivo* skin-nerve preparation. We were able to record from 220 myelinated afferent fibers and 72 unmyelinated C-fibers with receptive fields in the control uninjured plantar skin as well as plantar skin of CCI mice. We will present evidence that changes in the mechanosensitivity of sensory fibers innervating the glabrous skin may contribute to the symptoms of neuropathic pain.

NATURAL HISTORY STUDY IN HEREDITARY SENSORY NEUROPATHY TYPE 1 (HSN1): IMPROVING THE RESPONSIVENESS OF OUTCOME MEASURES

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HSN1 secondary to *SPTLC1/2* is a rare slowly progressive neuropathy resulting in marked sensory loss, especially nociception and significant motor deficit. Despite most of the patients having the same C133W mutation in *SPTLC1*, there is marked heterogeneity in the phenotype. L-serine oral supplementation has been suggested as potential therapeutic candidate however the lack of outcome measures is a major limiting factor in the initiation of a clinical trial. We undertook a natural history study to identify outcome measures that are responsive enough to be used in a clinical trial. The assessments used were CMT Neuropathy score (CMTNS version 2 and CMTNS version 2 Rasch modified), MRI of calves and thighs, computerised myometry, quantitative sensory testing (QST), comprehensive neurophysiological assessment, proximal thigh skin biopsy for intra-epidermal nerve fibre density (IENFD), plasma dSL levels and patient based questionnaires (Neuropathic Pain Symptom

Inventory and SF-36v2). Standardised Response Mean, SRM (mean change/standard deviation of change) was used to compare responsiveness between tests. 35 patients were recruited: 31 with *SPTLC1* (C133W) and 4 with *SPTLC2* mutations. When analysed as a whole cohort, proximal calf MRI fat fractions showed the most significant change over 12 months. IENFD, plasma dSL levels, NPSI and SF-36v2 showed minimal change or the change was not in the clinically expected direction. For subsets of the remaining assessments which showed the highest responsiveness, the cohort was sub-divided into mild-moderate (CMTNS ≤20) and severe (CMTNS>20) subgroups. In the mild-moderate subgroup, the greatest improvement in responsiveness was seen in computerised myometry (ankle plantarflexion: SRM=-0.80 and ankle eversion: SRM=-0.79). In the severe subgroup, QST (Vibration detection thresholds on hands: SRM=-0.80 and face: SRM=-0.92 and Pressure pain threshold on the face: SRM=1.27) and proximal calf MRI fat fractions (SRM range=0.73-1.26) showed the greatest improvement. Focusing on subgroups classified according to disease severity improved the responsiveness of some tests into the highly responsive range with MRI still being the best outcome measure. This will reduce the number of participants required to power a clinical trial and might be a possible solution for designing a clinical trial for a rare, slowly progressive disease with a heterogeneous phenotype.

HUMAN IPSC DERIVED SENSORY NEURON MODEL OF HEREDITARY SENSORY NEUROPATHY TYPE 1 (HSN1)

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HSN1 secondary to *SPTLC1/2* mutation is a slowly progressive sensory motor neuropathy leading to profound sensory loss with variable but often severe motor deficit. The genes *SPTLC1* and *2* encode for the essential enzyme serine palmitoyltransferase (SPT) which catalyses the rate limiting step in the sphingolipid de-novo biosynthesis. Mutations in these two genes alter the substrate specificity of SPT leading to the synthesis and accumulation of atypical metabolites called 1-deoxysphingolipids (1-deoxySL). Plasma levels of 1-deoxySL are raised in HSN1 patients. Deoxysphingolipids have been shown to be toxic in avian and by our group, in mammalian primary DRG and motor neuron cultures. Firstly, this study looked at the effects of 1-deoxySL on the survival and neurite integrity of human iPSC derived sensory neurons following exposure to different concentrations of deoxysphingolipids. Later, we determined if there was autonomous 1-deoxySL production in HSN1 patient iPSC derived sensory neurons. Sensory neurons were differentiated from human iPSCs using a combination of small molecular inhibitors. Deoxysphingolipids were found to be neurotoxic in this model after 48 hours of treatment. In control lines, there is a significant reduction in neuronal survival following treatment with both 1-deoxysphinganine (1-deoxySA) and 1-deoxymethylsphinganine (1-doxmethSA). A clear dose-dependent increase in the expression of the axonal injury marker, ATF3, is seen with both 1-deoxysphngoid bases. In both instances, 1-deoxySA is more neurotoxic than 1-doxmethSA, which is similar to the findings in avian and mammalian primary neuronal cultures. Autonomous 1-deoxySL production is seen in iPSC derived neurons obtained from three different HSN patients with the levels being significantly greater than that seen in multiple control lines. This is the first study to demonstrate that human iPSC derived sensory neurons can be used as an in-vitro model for HSN1, providing a great opportunity both to probe the pathomechanisms mediating deoxysphingolipid toxicity and to test potential therapeutic agents.

ANTI-NFASC155 NEUROPATHY: A RELAPSING-REMITTING NEUROPATHY?

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Recent studies have demonstrated an association between autoantibodies directed against antineurofascin-155 (anti-Nfasc155) and a subpopulation of CIDP patients characterized by sensory ataxia, tremor and poor response to IVIg treatment. Here we report on the clinical features of three patients who developed acute changes in their phenotype during the course of their neuropathy, a potential clue to recognize a neuropathy with predominantly humoral dysimmunity. Case reports: Our index patient had developed sensory changes over 6 weeks, followed by irregular locomotion, and muscle weakness with general areflexia. A first run of IVIG improved the patient in a week, but he relapsed within 10 days. A second IVIG course with prednisone again normalized deficits within 10 days. IVIG runs and rituximab were still necessary to treat a 2nd, and then a 3rd relapse before obtaining complete improvement. The course of the neuropathy was 5 months. Two other patients were encountered with more chronic courses but in whom periods of worsening or improvement suggested a relapsing-remitting neuropathy, either spontaneously or following immunomodulating treatments. In all three, extensive work-ups were negative, anti-Nfasc155 IgG4 were positive, and detailed repeat nerve conduction studies demonstrated fluctuating

conduction blocks. Discussion: Our report underscores that in chronic CIDP patients a relapsing-remitting course could be encountered as a key feature of anti-Nfasc155 neuropathy. This not yet described characteristic course could be of value when deciding using rituximab instead of immunomodulating treatments.

INVESTIGATION OF SERUM ANTIBODIES AGAINST GLYCOLIPIDS AND GLYCOLIPID COMPLEXES IN IMMUNE-MEDIATED NEUROPATHIES BY COMBINATORIAL GLYCOARRAY

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Anti-glycolipid antibodies are often detected in sera from patients with autoimmune neuropathies, such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN). Not only individual glycolipid antigens but also mixtures of two different glycolipids (glycolipid complexes) are sometimes recognized by serum antibodies. To investigate antibody activities against large number of glycolipid complexes in serum samples from patients with GBS, MMN, and CIDP, we examined IgM and IgG antibodies against 10 glycolipids [GM1, GM2, GD1a, GD1b, GQ1b, GalNAc-GD1a, LM1, galactocerebroside (Gal-C), asialo-GM1 (GA1), and sulfatide] and 45 glycolipid complexes consisting of two different glycolipids listed above, by using combinatorial glycoarray. Serum was obtained from 100 patients with GBS, 100 patients with CIDP and 24 patients with MMN, all in the acute or relapsing phase. Serum was also obtained from 30 healthy controls and 99 patients with other neurological diseases. We investigated the relationships between the clinical features and presence of those antibodies. High titers of IgG antibodies were detected almost exclusively in GBS patients. In contrast, IgM antibodies were frequently present in MMN and GBS. Among the anti-glycolipid complex antibodies in GBS, anti-GM1/sulfatide, anti-GA1/sulfatide, anti-GM1/GD1a, and anti-GQ1b/sulfatide IgG antibodies were common (20, 19, 17, and 14 patients, respectively). IgG antibodies against antigens containing GM1 were significantly correlated with pure motor GBS ($p < 0.01$) and those against antigens containing GQ1b were significantly correlated with GBS with ophthalmoplegia ($p < 0.01$). In seven of the 14 patients with anti-GQ1b/sulfatide complex antibodies, the antibodies were specific to the GQ1b/sulfatide complex rather than the individual GQ1b and suldfatide antigens. Moreover, four patients did not have antibodies other than those to the anti-GQ1b/sulfatide complex. In patients with MMN, IgM antibodies to antigens containing GM1 or GalNAc-GD1a were present in 50% and 37.5%, respectively. Glycoarray is efficient for detecting antibodies against numerous glycolipid complexes in immune-mediated neuropathies. We need further investigations on other immune-mediated diseases using larger number of antigens.

JAPANESE ECULIZUMAB TRIAL FOR GUILLAIN- BARRÉ SYNDROME (JET-GBS)

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Guillain-Barré syndrome is a monophasic immune-mediated neuropathy, but a substantial number of patients with severe disease have poor recovery, even if treated with immunoglobulin. Recent studies suggest that complement activation plays a pivotal role in GBS-associated axonal degeneration, and eculizumab is a monoclonal antibody that specifically binds to complement component 5 and inhibits complement activation. JET-GBS is an investigator-led, phase 2, randomized, placebo-controlled trial conducted in 13 hospitals, This trial aims to investigate the safety and efficacy of eculizumab for treatment of severe GBS. 34 patients were randomly assigned (2:1) to treatment with immunoglobulin plus either eculizumab (900 mg/day; n=23) or placebo (n=11) once weekly for 4 weeks. The primary outcome measures are safety and efficacy (the proportion of subjects who regain their ability to walk independently at Week 4). The secondary outcome measures included the proportion of subjects who were able to walk independently at Week 24, and other measures such as MRC sum scores, nerve conduction parameters. Enrollment for the trial began in August 2015, and follow-up of the last patient was completed in October 2016. Analyses will be made in April 2017, and the results will be presented at this meeting. This trial is registered with ClinicalTrials.gov Identifier: NCT02493725, and funded by the Japanese Agency for Medical Research and Development, and Alexion Pharmaceuticals Inc.

CLINICAL AND PATHOLOGICAL FEATURES IN FOUR PATIENTS WITH ANTI-NEUROFASCIN 155 IGG4 ANTIBODY-POSITIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Neurofascin 155, a paranodal protein in peripheral nerve, is a target antigen for autoantibodies in a subset of chronic inflammatory demyelinating polyneuropathy (CIDP). Anti-neurofascin 155 antibody-positive CIDP is characterized by onset at

younger age, tremor, and refractoriness to IVIg. We have treated four patients with anti-neurofascin 155 antibody-positive CIDP at Kindai University Hospital. Anti-neurofascin 155 antibody was detected by both ELISA and cell-based assay in those patients. IgG subclass was predominantly IgG4 in all four cases. The median age of the patients at admission was 39.5 years [range: 30-43 years]. Among the four patients, three had tremor, and two had severe cerebellar ataxia. Cerebrospinal fluid protein levels were remarkably increased [median: 494.5 mg/dl, range: 216-882 mg/dl]. Although IVIg treatment was administered in all four patients, the responses were poor or partial. In contrast, plasma exchange (PE) was performed in all four patients and the clinical symptoms dramatically improved in two of them. Corticosteroids were also effective in those two patients. Sural nerve biopsy was performed in all four patients. Although sensory nerve action potentials of the sural nerves from those patients were not evoked, the transverse semithin sections of sural nerves from three patients revealed only slight or mild loss of myelinated fibers. Partial paranodal demyelination was observed in teased-nerve fibers from three patients. In addition, abnormal paranodal lesions such as loss of the transvers bands were observed by electron microscope in all four patients. Those electron microscopic findings were not observed in control patients with anti-neurofascin 155 antibody-negative CIDP. Anti-neurofascin 155 IgG4 antibody-positive CIDP shows distinctive clinical and pathological features.

PLEXIC MRI AND POSITRON EMISSION TOMOGRAPHY (PET) MERGE: A NEW TOOL FOR THE INVESTIGATION OF PERIPHERAL NERVES?

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Study of the proximal portion of the peripheral nervous system (PNS) is difficult because less accessible to electrophysiological exploration and biopsy. The indications of MRI are increasing in proximal neuropathies to analyse morphology of the roots, plexus and proximal nerves: integrity of the nerve bundle, inflammation or infiltration of these structures. PET-computed tomography (PET-CT) can detect infiltration of the proximal segments of the PNS, with hypermetabolism of roots, plexuses and large nerve trunks. PET-CT is also useful in detection of solid neoplasm which can infiltrates PNS and primary nerve sheath tumors. However, spatial resolution of PET -CT scan is limited to explore the roots and plexuses for moderate hypermetabolisms. We believe that a mild hypermetabolism could be highlighted in inflammatory neuropathies or in mild tumor infiltrations. We performed a fusion of whole body PET (performed because of suspected neoplasia) and plexus MRI (PET-MRI) images in ten patients with a peripheral neuropathy for which we suspected proximal involvement. The PET-CT and MRI were first read separately, then with merge of the images by a nuclear physician and a neuroradiologist. Five out of ten patients presented with hypermetabolism of PNS (HMPN+) on PET-MRI: root (n=4), and/or dorsal root ganglia (n=2). Median SUL of lesions was 1.9. Among the HMPN+ patients: hypermetabolism was already apparent on PET-CT in 2 cases, the merge invalidated abnormalities seen on PET-CT in 2 patients and MRI detected additional lesions, not visible on PET-CT, in one patient. All HMPN+ patients had hypersignal and or hypertrophy of PNS on MRI either diffuse (n=4), or multifocal (n=1). Among HMPN- (no hypermetabolism) 2 out of 5 (40%) had abnormal MRI (1 multifocal and 1 diffuse). Gadolinium enhancement was found in all patients receiving gadolinium in the HMPN+ (n=4) and only in 2/5 patients in the HMPN- group. Final diagnoses of HMPN+ patients were neurolymphoma in one (20%), and idiopathic CIDP in the 5 others (80%) with histological proof on nervous root biopsy in one of them. Final diagnosis in HMPN- patients was CIDP in 4 out of 5 and sequelae of neuropathy in relation to lymphoma without relapse for the last one. CIDP was more disabling (ONLS≥4) in HMPN+ than in HMPN- group 100% vs. 20%. PET-MRI could be helpful to detect a proximal inflammation of the PNS, and to plan further testing. Further studies are needed to evaluate the prognostic value of HMPN+.

THE DEVELOPMENT OF NEUROPATHY IN A MOUSE MODEL OF CMT2E - SEQUENTIAL NERVE CONDUCTIONS

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Heterozygous *Nefl*$^{N98S/+}$ mutant mice are the first animal model of a Charcot-Marie-Tooth disease 2E (CMT2E). People with this mutation have a severe, early onset axonal neuropathy. Axons in the mutant mice have reduced number of neurofilaments and decreased diameters. They also show early onset of tremor and abnormal hindlimb clasping behavior. We measured the compound action potentials (CAPs) from tails every 4 weeks from the same cohort of *Nefl*$^{N98S/+}$ mutant mice and their WT littermates from 8 to 48 weeks. Even at the age of 8 weeks, the amplitude of mutant CAPs was only ~20 % of WT CAPs (29 ± 3.7 microV, n=15 vs 142 ± 10.7 microV, n=15), and the CAPs stayed substantially smaller than those in WT mice for 48 weeks (40 ± 6.0 microV, n=13 vs 263 ± 26.7 microV, n=15). The conduction velocity and the duration of CAPs in mutants were slower and wider compared to those of WT. Separate cohorts of mice (n=6 mutants and n=6 WT) were sacrificed at different time points for analysis by light microscopy. In caudal nerve of mutant mice, the number of axons was significantly reduced compared to that of WT at 8 weeks and, by 48 weeks, it was reduced more than 50%. This model system may be useful for preclinical studies of treatments for CMT2E since the animals show progressive neuropathy over

48 weeks, which can be objectively measured electrophysiologically and anatomically.

ATP1A1 REPRESENTS A SIGNIFICANT NOVEL DOMINANT CMT2 GENE

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Despite more than 90 CMT genes identified today, at least 50% of CMT2 patients do not carry a mutation in any of these genes. Progress in gene identification in recent years suggests that there are still many more CMT2 disease genes to be discovered; however, it has become rare to gather support from multiple large families that allow for conclusive linkage analysis. We have studied multiple extended dominant CMT2 families with linkage support for a gene at chromosome 1p13.1. Originally a Czech family yielded a two point LOD score of 2.4 at this locus and a family from Southern Italy showed a LOD score of 3.2. Whole exome sequencing of multiple family members identified missense mutations in the gene ATPase Na+/K+ Transporting Subunit Alpha 1 (ATP1A1). ATP1A1 has not been associated with human diseases thus far. In expression studies on teased fiber preparations we already confirmed predominant expression in the nodes of Ranvier of peripheral nerves. Through collaborative efforts in the Inherited Neuropathy Consortium and beyond we identified five additional multigenerational families via exome or Sanger sequencing resulting in a total of seven unique segregating missense changes: Leu48Arg, Ile592Thr, Ala597Thr, Asp601Phe, Pro600Ala, Pro600Thr and Asp811Ala. Five of these mutations fall into a remarkably narrow motif associated with the sodium binding structure of ATP1A1, flanking the flexible hinge motif. Functional studies in different model systems (mammalian cell lines, Xenopus oocytes, patient fibroblast lines) are underway to determine whether a loss or a dominant gain-of-function represents the disease mechanism. Taken together, we show strong support for a major new dominant CMT2 gene, ATP1A1. This finding represents a new pathway and an attractive new target for therapy development in axonal CMT.

SURGICAL MANAGEMENT OF FOOT AND ANKLE DEFORMITIES IN CHARCOT MARIE TOOTH DISEASE: RESULTS OF A PROSPECTIVE STUDY

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Charcot-Marie-Tooth (CMT) Disease is the most common inherited peripheral neuropathy. Foot deformities are frequent complications and orthopaedic surgery is often required. However there are no evidence based guidelines on the type or timing of the surgery. Only few studies have described the long-term results of surgical procedures and evidence regarding optimal surgical management of these patients is lacking. We prospectively studied surgical management of CMT patients attending our centre. We collected data and assessed CMT patients before and after surgery. Data included: history of ankle instability, pain, skin condition, details of physiotherapy and orthotic management, assessment of lower limb strength, Charcot-Marie-Tooth Examination Score (CMTES), Foot Posture Index, ankle dorsiflexion range of movement and specific questionnaires (foot index and Manchester-Oxford foot questionnaire, modified fatigue severity scale and modified falls efficacy scale), details of surgical procedures. Patients were assessed yearly after surgery. So far 23 patients (16 males and 7 females, age range 20 – 58) have been evaluated prior to surgery. All patients but one had genetically confirmed CMT (18 CMT1A, 3 CMTX, 1 CMT4A). 12 patients have been assessed after 1 year, 6 patients after 2 years, 7 patients after 3 years and 1 patient after 4 years from surgery. A wide range of surgical procedures were performed by one dedicated orthopaedic surgeon. Preliminary results showed reduction of number of falls in 5/9 (55%) patients and improvement of callosities in 6/12 (50%) patients at 1 year follow up. There was also significant improvement of alignment of the operated foot ($p=0.02$) and pain ($p=0.003$). There were no significant changes in measures of strength and ankle range of motion. Further analysis on a larger number of patients will be important to determine the long-term outcome of surgery. Data acquired from this study will help develop orthopaedic intervention guidelines and identify areas for further research.

EMG PATTERNS IN FAMILIAL AMYLOIDOTIC POLINEUROPATHY (FAP) DUE TO TTR MUTATIONS

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FAP associated to TTR mutations is defined as a length-dependent axonal sensory and motor polyneuropathy that at early stages affects mainly the small nerve fibers, associated to autonomic and thermo-algesic sensations. The expected EMG pattern was that of an axonal sensory and motor polyneuropathy, but in fact several unexpected patterns may be found. In this study we present the results found in a Brazilian population with TTR mutation. Patients were divided in three groups: TTR-Met30 of early onset, TTR-Met30 of late onset and TTR non-Met30.
In the first group (TTR-Met30 of early onset), 10 (34.5%) examinations were normal, 12 (41.4%) were axonal, 5 were demyelinating fulfilling PIDC criteria, one suggested a predominately motor polyneuropathy and the final one presented a lower motor neuron disease pattern. In the second group (TTR-Met30 of late onset), 4 (44.4%) had an axonal pattern, 2 (22.2%) had an intermediate CV, 1 (11.1%) had a demyelinating pattern, 1 had a lumbossacral pattern and the final one had no definite pattern. Among the non-TTR Met30, two patients had the TTR -Asp38Tyr, one presented an axonal pattern, while the second presented initially an axonal pattern, that changed to a demyelinating pattern in the second examination. Patients with Ile107Val mutation presented an axonal neuropathy associated to CTS. Most patients with demyelinating or intermediate pattern were treated with corticosteroids or IVIg, with no satisfactory results. This small series of patients shows clearly that FAP-TTR is associated to several EMG patterns in addition to the expected sensory and motor axonal polyneuropathy. This variability is present in the same family and in the same patient in different occasions. Clinicians should be alert to these possibilities to do not delay diagnosis and treatment. Identifying the mechanisms involved in this variability could improve our knowledge of this intriguing disease.

DE-NOVO SUBCUTANEOUS IMMUNOGLOBULIN G FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY. A SINGLE CENTRE EXPERIENCE OF 3 PATIENTS

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Subcutaneous immunoglobulin (ScIg) has evidence from small trials for its use following Intravenous IgG (IVIG) loading in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Potential advantages of ScIg include stable IgG levels and reduced complication rates. ScIg de novo can be considered as IgG levels gradually rise with subcutaneous delivery and maybe beneficial for patients for whom complications are a concern. We present 3 cases of CIDP who were initiated on subcutaneous immunoglobulin G (2g/kg/month, 20% ScIg, Hizentra, CSL Behring) following corticosteroids; without Intravenous IgG loading. Patient 1 is 67 year old with a history of IHD with a progressive lower limb sensory changes and sensory ataxia over 3 years. Neurophysiology confirmed sensory demyelinating changes. He did not respond to corticosteroids. Concerns were raised about the potential risk of adverse cardiac events with IV immunoglobulin. ScIg therapy was introduced at 30g weekly. Initial therapy has been well tolerated and objective measures (RODS-CIDP score, JAMAR Grip strength, 9 hole PEG) have remained stable through initiation, and at 3 months. Patient 2 is 65 yr old male with a past history of Branch Retinal Vein Thrombosis. He developed a sensorimotor polyneuropathy over 2 years with neurophysiology fitting EFNS criteria for CIDP. Given concerns regarding previous thrombosis, a trial of ScIg was given at 34g/week, with resolution of sensory ataxia and improvement in objective markers (JAMAR Grip strength, RODS-CIDP score, 9 hole PEG) at 3 months. Unfortunately an adverse event occurred of an urticarial skin reaction. Patient 3 is a 55 yr old male who presented with motor predominant CIDP. There was no response to corticosteroids but improvement following plasma exchange. Due to a past history of transient ischaemic attack, ScIg was started. There has been a positive response after 3 months with improvement in walking distances and stable objective markers (RODS-CIDP score, Grip and Pinch strength). Our cohort remained neurologically stable during initiation of ScIg, with 1 adverse reaction. Our experience would support further trials in this area regarding the efficacy of ScIg compared to IVIg in both the short and long term.

CHARACTERIZING IN VITRO MODELS OF TYPE 2 DIABETIC PERIPHERAL NEUROPATHY

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Diabetic peripheral neuropathy is the most common and debilitating complication of diabetes and it is associated to neuropathic pain and non-traumatic amputations. Despite the economic burden and human costs, nowadays there is not a specific treatment to cure diabetic peripheral neuropathy. Hyperglycaemia and dyslipidemia-mediated oxidative and endoplasmic reticulum stress has been linked to diabetic peripheral neuropathy, among other altered pathways. In order to study in more detail the molecular mechanisms that lead to the development of diabetic peripheral neuropathy we set up in vitro models of the disease using NSC-34 (motoneurons)

and Med17.11 (sensory neurons) cell lines or primary cultures of dorsal root ganglia and motoneurons exposed to saturated fatty acids. It has been reported that palmitic acid is able to induce endoplasmic reticulum stress and oxidative stress in multiple cell types including Schwann cells and myenteric neurons, resulting in a good model of dyslipidemia-mediated stress. Here we found that palmitate induces upregulation of the molecular chaperone BIP/Grp78 and the CCAAT-enhancer-binding protein homologous protein (CHOP) mRNAs and a dose-dependent downregulation of the apoptosis marker Bcl-2 in primary cultures. Moreover, palmitic acid induces loss of neuron dendrites and cell death at high doses and upregulation of heme oxygenase (HO-1) and CHOP at lower doses in the NSC-34 cell line. We are currently characterizing multiple molecules implicated in oxidative stress, endoplasmic reticulum stress and inflammation pathways in these cell types to find new therapeutic targets to treat type 2 diabetic sensorimotor polyneuropathy, that will be subsequently validated in the Db/Db mouse model by pharmacological or gene therapy strategies.

NOSOCOMIAL TREATMENT-INDUCED NEUROPATHY OF DIABETES MELLITUS (TIND)?

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Treatment-Induced Neuropathy of Diabetes Mellitus (DM) (TIND) is an acute painful peripheral neuropathy and autonomic dysfunction that occurs within 8 weeks of tight glycaemic control. Therapy with either insulin or oral hypoglycaemic agents (OHGA) may result in TIND. The quantum and rate of decline in HbA1c predicts development and severity of TIND. Both type I and II DM patients are prone to this iatrogenic complication. Besides the expected morbidity associated with painful somatic and autonomic neuropathy, TIND patients also develop life-threatening eye complications such as maculopathy. With greater awareness, we picked up at least 3 typical cases of TIND in recent few months. However, there was a fourth possible TIND case, whom we feel deserves special attention. The circumstances surrounding this case are common and may go under-recognised in acute hospitals. A 66 year-old man with 11-year history of poorly controlled Type II DM was admitted with a partial left middle cerebral artery stroke. One month before admission, his HbA1c was 14.4%. His hospitalization was prolonged because of his considerable disability that required rehabilitation. He stayed 11 weeks. His blood sugar was difficult to control with hyperglycaemic episodes requiring 2 OHGAs and insulin. The highest capillary blood glucose recorded was 20 mmol/L. He also had 3 episodes of hypoglycaemia. Three weeks into hospitalization, he developed severe orthostatic hypotension. He came to our attention two months later when he was sent for autonomic screening tests for severe postural hypotension, in spite of therapy with fludrocortisone and midodrine. His HbA1c was 9.6%. He had marked orthostatic hypotension suggestive of sympathetic dysfunction. We were not able to discern if he had a painful neuropathy because of his aphasia. There was no recent ophthalmology review. We suggested a diagnosis of possible TIND. He was discharged with lower doses of OHGA. However, 1 day after discharge, he attended the emergency department for a syncopal episode. This case raises intriguing questions on the safety of glucose control paradigms commonly employed in patients with acute stroke and myocardial infarction as well as the possible role of major fluctuations in blood glucose in the development of TIND.

A RARE CASE OF NEUROFIBROMATOSIS PRESENTING WITH DEMYELINATING POLYNEUROPATHY

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The occurrence of peripheral neuropathy by a tumor within or compressing a nerve in neurofibromatosis (NF) type 1 and 2 is relatively well known. However, NF presenting with demyelinating polyneuropathy unrelated to tumor masses is rarely reported. We report a rare presentation of an NF patient with demyelinating polyneuropathy of subacute onset. A 30-year-old woman was referred to our hospital with paresthesia on both limbs 5 months before. She was healthy and had no family history. The symptoms worsened over the next 3 months, tremor and weakness in both limbs occurred. Although she treated as a chronic inflammatory demyelinating polyneuropathy (CIDP) with intravenous steroid and immunosuppressant in another hospital, symptoms were getting worse. Bifacial numbness and left eyeball pain occurred 2 weeks ago and she visited our hospital. On neurologic examination, bilateral facial sensory hypoesthesia and symmetrical both limbs weakness (MRC grade IV+) were observed. Decreased touch and pinprick sensation on both limbs were observed like stocking-glove distribution. The reflexes were sluggish. On nerve conduction study, sensorimotor demyelinating polyneuropathy with conduction blocks and temporal dispersions was observed. Bilateral R1, R2 responses were prolongation on facial blink test. MRI of cervical spine and brain revealed contrast enhancing tumor-like enlargement of multiple nerve roots and cranial nerves. Nerve biopsy was performed on right supraorbital nerve, neurofibromatous changes were observed. The symptom deterioration was stopped without treatment. Gene test dose not revealed NF type 1 and 2. On review of the literature, polyneuropathy in NF patient can result from tumor masses within the proximal nerve roots, or along the peripheral nerve, or in the extramedullary lesion affecting neighboring nerve roots. Thus, axonal type polyneuropathy and focal amyotrophy have been reported in NF. Demyelinating polyneuropathy has not been reported before in our knowledge. Although the etiology of demyelinating polyneuropathy in NF requires further clarification, some authors claim that

unknown local toxic or metabolic influences of the endoneurial pathological cells on adjacent nerve fibers. In this patient, atypical symptoms were observed in CIDP such as cranial nerve involvement and stocking-glove sensory distribution. In this case, a nerve biopsy can be helpful the accurate diagnosis.

COEXISTENCE OF ACUTE DISSEMINATED ENCEPHALOMYELITIS AND GUILLAIN-BARRÉ SYNDROME WITH IG G ANTI-GT1A ANTIBODY POSITIVITY

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Acute disseminated encephalomyelitis (ADEM) is an uncommon post-infectious inflammatory demyelinating disorder of central nerve system, while Guillain-Barre syndrome (GBS) is a prototype of acute post-infectious peripheral neuropathy. Previous reports regarding the coexistence of these relatively rare diseases suggest that certain immunogenicity within central and peripheral nerves may share a common autoimmune process during the disease course. A previous healthy 20 years old man was admitted because of fever, headache, nausea and myalgia in department of infectious disease. Two weeks before admission, he suffered from watery diarrhea for 3 days and spontaneously recovered. At initial presentation, he had high fever(39℃), headache and myalgia and intermittent horizontal diplopia. A few days after admission, he began to complain of drowsy mentality, bilateral extremities weakness, especially lower limbs, dysarthria, bilateral facial paralysis, urinary retention, dyspnea. On neurologic examination, he had mildly drowsy mentality, symmetric muscle weakness scoring 4 of 5 on bilateral hip, knee flexion and finger extension, but he had no sensory symptoms. He showed gazed evoked nystagmus with no extraocular muscle palsies. Deep tendon reflexes were not present. Pulmonary function test revealed a severe restrictive pattern. CSF studies disclosed a dissociative increase of protein contents (66mg/dL) without pleocytosis. Anti ganlioside antibody assay identified an anti-GT1a IgG positivity in his serum. Nerve conduction study (NCS) showed prolonged motor terminal latencies and slow motor conduction velocity on multiple nerves. In contrast, sensory NCS revealed no abnormal findings. Imaging studies unexpectedly revealed apparently symmetrical lesions across bilateral brainstem and basal ganglia suggesting a diagnosis of ADEM. After both IVIG and high dose steroid treatment, he remarkably recovered from disturbed mental state and motor weakness. About 1month after the symptom onset, he could walk with assistant aid and discharge to other hospital for rehabilitation. Our case suggest that certain component of autoimmunity simultaneously result in both CNS and PNS inflammation. Specific immunological mechanism is remained to be elucidated. Although we could not conclude whether cellular component or humoral component is dominant for our case, the presence of anti GT1a antibody suggest a role of humoral mechanisms.

NEUROPATHY AND PRIMARY HEADACHES DO NOT AFFECT THE SAME SUBGROUPS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

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Peripheral Neuropathies and Primary Headaches are common in patients with IBD (Oliveira, Inflamm Bowel Dis 2008;14:389; Gondim, Inflamm Bow Dis 2015;21:2123). The aim of this study is to evaluate whether peripheral neuropathies and headaches affect the same subgroups of patients with IBD. Since 2004, we have established a cohort study to evaluate the prevalence and incidence of neurological diseases in patients with IBD. Over a period of 2 years, all patients with IBD (either Crohn´s disease or ulcerative colitis) were invited to participate in a study designed to evaluate the risk factors for the presence of headaches and peripheral neuropathy in IBD. A separate group of control patients (age-matched relatives of IBD patients) was also formed. After a clinical interview and neurological examination, patients were invited to undergo skin wrinkling test (SWT) to evaluate small fiber function and/or electromyography. Headaches were present in 49.3% of the patients with IBD, and were more common in patients with ulcerative colitis than in control patients ($P<0.05$). Migraine comprised 61.2% of all cases of headache and was more prevalent in patients with Crohn´s disease than control patients ($P<0.05$). Tensional headaches were also common affecting 25.4% of the IBD patients. Electromyography was abnormal in 21.1% of the IBD patients tested (19/90). SWT was abnormal in 42.2% of the IBD patients tested (38/90). 14.4% of the IBD patients had abnormal SWT but had no neuropathy symptoms. Patients with abnormal SWT or EMG were not more likely to have headaches ($P=0.30$ and 0.87, respectively). Overall, patients with symptomatic polyneuropathy were not more likely to have headache ($P=0.48$). Patients with abnormal SWT or EMG were also not more likely to have migraine ($P=0.43$ and 0.28, respectively). Patients with abnormal SWT or EMG were also not more likely to have tension-type headache ($P=0.31$ and 0.62, respectively). In summary, although highly prevalent in this population of Brazilian IBD patients, primary headaches and neuropathy do not affect the same subgroups of IBD patients. Further studies are necessary to understand the mechanisms of both conditions in IBD patients.

NEUROPATHY AND PRIMARY HEADACHES DO NOT AFFECT THE SAME SUBGROUPS OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

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Peripheral Neuropathies and Primary Headaches are common in patients with IBD (Oliveira, Inflamm Bowel Dis 2008;14:389; Gondim, Inflamm Bow Dis 2015;21:2123). The aim of this study is to evaluate whether peripheral neuropathies and headaches affect the same subgroups of patients with IBD. Since 2004, we have established a cohort study to evaluate the prevalence and incidence of neurological diseases in patients with IBD. Over a period of 2 years, all patients with IBD (either Crohn´s disease or ulcerative colitis) were invited to participate in a study designed to evaluate the risk factors for the presence of headaches and peripheral neuropathy in IBD. A separate group of control patients (age-matched relatives of IBD patients) was also formed. After a clinical interview and neurological examination, patients were invited to undergo skin wrinkling test (SWT) to evaluate small fiber function and/or electromyography. Headaches were present in 49.3% of the patients with IBD, and were more common in patients with ulcerative colitis than in control patients ($P<0.05$). Migraine comprised 61.2% of all cases of headache and was more prevalent in patients with Crohn´s disease than control patients ($P<0.05$). Tensional headaches were also common affecting 25.4% of the IBD patients. Electromyography was abnormal in 21.1% of the IBD patients tested (19/90). SWT was abnormal in 42.2% of the IBD patients tested (38/90). 14.4% of the IBD patients had abnormal SWT but had no neuropathy symptoms. Patients with abnormal SWT or EMG were not more likely to have headaches ($P=0.30$ and 0.87, respectively). Overall, patients with symptomatic polyneuropathy were not more likely to have headache ($P=0.48$). Patients with abnormal SWT or EMG were also not more likely to have migraine ($P=0.43$ and 0.28, respectively). Patients with abnormal SWT or EMG were also not more likely to have tension-type headache ($P=0.31$ and 0.62, respectively). In summary, although highly prevalent in this population of Brazilian IBD patients, primary headaches and neuropathy do not affect the same subgroups of IBD patients. Further studies are necessary to understand the mechanisms of both conditions in IBD patients.

SENSORY GUILLAIN BARRE SYNDROME

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The classic Guillain Barré syndrome (GBS) is characterized by motor weakness, hyporreflexia, but limited sensory deficits. Sensory variants involving either small or large fibers or both are unusual and represent a diagnostic challenge. We described 6 patients presenting with the sensory variant of GBS and retrospectively analyzed the clinical and electrophysiological findings of patients fulfilling the criteria for Sensory GBS according to Oh et al. criteria. Six patients were identified (mean age 38 years: range 15- 54 years). Four had a previous infection. They all consulted due to distal painful paresthesias and allodynia. On examination the 6 patients presented normal strength and normal cranial nerves through the course of the disease with reduced knee and ankle reflexes in 3 patients. Distal hyperesthesia to pinprick was identified in 3 and one of them additionally had hyperhidrosis and constipation. Two additional patients presented hypoesthesia to pinprick and temperature. One patient had distal proprioceptive sensory loss with sensory ataxia. CSF albumin cytological dissociation was present in 3 patients. Nerve conduction studies (NCS) identified a sensory motor demyelinating neuropathy in 2 patients. Among the 4 with normal NCS, 2 had abnormal cold and warm threshold in their QST evaluation. All patients received symptomatic treatment for the neuropathic pain and only two IvIg therapies. Longstanding pain, fatigue or both were persistent findings in 5 patients after a mean follow up of 6 months. In conclusion the sensory variant of GBS is both an infrequent presentation and a diagnostic challenge. Longstanding pain and fatigue are common persisting findings.

INTERNATIONAL ZIKA VIRUS RELATED GUILLAIN-BARRÉ SYNDROME OUTCOME STUDY (IGOS-ZIKA): A CASE-CONTROLLED STUDY

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The epidemic of Zika virus (ZIKV) throughout the Americas and Asia, and the subsequent rise in reported cases of Guillain-Barré syndrome (GBS) caused worldwide concern. As of January 2017, 76 countries have reported evidence of mosquito-borne ZIKV transmission and in 16 of these countries, a sudden increase of GBS has been reported. Moreover, case studies and a case-control study further indicate that ZIKV may trigger GBS. However, accurate diagnosis of both ZIKV and GBS in many of these studies is disputed, and a comprehensive description of the clinical phenotype of GBS related to ZIKV is lacking. The International GBS Outcome Study (IGOS) is a prospective observational study on the factors determining the onset, clinical course and outcome of GBS. At present, a research consortium of 150 centers from 19 countries has included 1461 patients in IGOS. Our aim is to investigate ZIKV-related GBS in IGOS as is already occurring in Colombia. In IGOS-ZIKA, data on clinical features and ancillary investigations will be collected in ZIKV endemic areas according to the IGOS protocol with some modifications. First, IGOS-ZIKA has a case-controlled study design to define the association between GBS and ZIKV and other arboviruses. Second, urine samples will be collected and additional questions on preceding events will be asked, focusing on arbovirus infections. Third, a more limited follow-up is required. Our aim is to recruit additional centers via the Inflammatory Neuropathy Consortium (INC) and centers in all arbovirus endemic regions that are willing to participate. The focus of IGOS-ZIKA will be on the accuracy of the diagnosis of both GBS and ZIKV and on defining the associated clinical phenotype, course and outcome. IGOS-ZIKA provides the opportunity to combine data and biobanks from various geographical regions using a standardized protocol and to compare these data with data and biosamples already collected in IGOS. Studying these cases will help to optimize diagnostics and care for GBS patients in arbovirus endemic countries and provides a unique opportunity to further understand the pathogenesis of GBS. Moreover, this study design and network can be used to adequately respond to other future viral epidemics related to GBS.

A COMPLEX HOMOZYGOUS MUTATION IN ABHD12 RESPONSIBLE FOR PHARC SYNDROME DISCOVERED BY NGS

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PHARC syndrome is an autosomal recessive neurodegenerative pathology leading to demyelinating Polyneuropathy, Hearing loss, cerebellar Ataxia, Retinis pigmentosa and early-onset Cataract. These various symptoms can occur at different ages, so that PHARC syndrome can be a differential diagnosis of Charcot-Marie-Tooth disease (CMT) associated with deafness. Only 13 ABHD12 mutations have been reported in 33 patients. We described the 14th mutation and compared our results to the literature data. We analysed by Next Generation Sequencing (NGS) strategy using a targeted CMT and associated neuropathies 92-gene panel the DNA of a 36-year old male who has suffered from demyelinating sensory and motor polyneuropathy and ataxia since the age of 15. Bilateral sensorineural deafness was diagnosed at the age of five. Bilateral congenital cataracts were operated on at the age of 28. A new large complex homozygous mutation, with one deletion of seven base pairs and one insertion of 38 base pairs, was detected. By analyzing our patient data and those of the literature, we evaluated that, in PHARC syndrome, sensorineural deafness always occurs as the first feature in late teens. The ophthalmological symptoms are cataracts that occur at a mean age of 25 yo and then retinis pigmentosa at a mean age of 29. Demyelinating sensory-motor polyneuropathy is the most variable characteristics, which occurs in the thirties. We report the first large complex homozygous mutation in PHARC syndrome, which is certainly under-diagnosed. Therefore, it seems interesting to include ABHD12 in the panels of the five symptoms, especially deafness ones.

REFINEMENT OF DIAGNOSTIC CRITERIA FOR CIDP BEYOND ELECTROPHYSIOLOGY: DATA FROM THE ITALIAN DATABASE FOR THE DIAGNOSIS AND THERAPY OF CIDP AND VARIANTS

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic disabling disease that often improves with immune therapy. To date, the most reliable diagnostic criteria for CIDP are the 2010 EFNS/PNS revised criteria, with a reported sensitivity of 80% and specificity of 90%. We implemented a web-based database to collect data from patients with CIDP followed by Italian Centers with expertise on CIDP to determine the frequency and characteristic of CIDP and it variants, the diagnostic criteria used for their diagnosis, the possible evolution into typical CIDP, the association with specific anti-nerve antibodies, and their response to therapy. All the patients were evaluated at the time of inclusion and will be followed for two years to monitor their outcome and response to therapy. By February 2017 we included 360 patients with CIDP and variants (227 men, 133 women), aged 12-86 years (median 59) with a mean disease duration of 8.2 years (range 0.5-52 years). Based on clinical symptoms, CIDP was defined as typical in 85% and atypical in 15%. The diagnosis of typical CIDP fulfilled EFNS/PNS criteria in 84% of the patients while nerve conduction studies were not diagnostic in 14% (grouped as clinical CIDP) or not available in 2%. We analyzed the frequency of supportive criteria for the diagnosis of CIDP in patients with clinical CIDP and found that increased CSF proteins, demyelination or cell infiltration on nerve biopsy and imaging abnormalities consisting with CIDP on US or NMR were present in 81%, 47% and 57% of the patients, respectively. A relapsing course was present in 79% of patients with clinical CIDP, increasing the reliability of the diagnosis for CIDP. In addition an improvement after one or more therapies was reported by 87% of the patients, with a positive response to IVIg in 74%, steroids in 52% and plasma exchange in 59%, similarly to what observed in patients fulfilling EFNS/PNS criteria. In 84% of the patients with clinical CIDP two or more supplementary criteria for CIDP were present. This study on a large population of patients is providing useful information that may help to revise the current diagnostic criteria for CIDP.

ACE-083, A LOCALLY-ACTING GDF/ACTIVIN LIGAND TRAP, AUGMENTS DORSIFLEXOR MUSCLE FUNCTION IN A MURINE MODEL OF CHARCOT-MARIE-TOOTH (CMT) DISEASE

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Charcot-Marie-Tooth (CMT) is the most common hereditary peripheral neuropathy and is characterized by demyelination and/or axonal damage of peripheral nerves and muscle weakness. Foot drop, steppage gait, and foot deformities are a typically seen in CMT patients. Consequently, falls are commonly reported in these patients. Improvement of dorsiflexor muscle function to prevent falls may improve quality of life and activities of daily living in patients with CMT. ACE-083, a locally-acting ligand trap that binds growth and differentiation factors (GDFs) and activins, has previously been shown to increase muscle mass and force in both Duchene muscle dystrophy (DMD) and amyotrophic lateral sclerosis (ALS) mouse models. In the current study, we evaluated the therapeutic effects of ACE-083 to improve muscle strength in the trembler (Tr-J) mouse model of CMT1A. These mice harbor a mutation in the peripheral myelin protein 22 (PMP22) known to cause CMT1A. Seven-month old (B6.D2-*Pmp22*$^{Tr\text{-}J}$/J) mice were administered ACE-083 (100µg, twice weekly) intramuscularly to one of the unilaterally tibialis anterior (TA) muscle for 4 weeks. The contractility of the TA muscle was evaluated during isometric contraction. All data were compared to the uninjected contralateral control hind-limb. After 4 weeks of ACE-083 treatment, TA muscle mass was increased by 63% ($p<0.01$) and its physiological cross-sectional area was increased by 69% ($p<0.01$). The increase in muscle mass correlated with an increase in strength, with maximum tetanic force and twitch force improved by 65% ($p<0.001$) and 44% ($p<0.001$), respectively. In addition, temporal properties during isometric contraction, such as maximum rate of contraction and relaxation, were accelerated by 46% and 56% respectively ($p<0.001$) in the ACE-083-treated TA muscle compared to its contralateral hind-limb. Pathological and biochemical assessment of ACE-083-treated mice showed enlarged myocyte area (+14%, $p<0.05$) and reduced atrogin-1 mRNA expression (-49%, $p<0.001$). Together, these results demonstrated that ACE-083 attenuates the degree of muscle atrophy and also improves muscle function in a mouse model of CMT1A. The current study provides proof of concept for the use of ACE-083 as a therapy for CMT to improve dorsiflexor muscle function and alleviate foot drop.

A RAT MODEL OF CMT2A DEVELOPS A PROGRESSIVE NEUROPATHY

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We have generated a rat model of Charcot-Marie-Tooth disease 2A (CMT2A) harboring the p.Arg364Trp *Mfn2* mutation, whose human counterpart results in a severe, early-onset axonal neuropathy. The mutation was made using zinc finger nuclease-mediated genome editing in fertilized rat eggs. A large cohort of mutant and WT littermates were characterized behaviorally and found to develop multiple motor deficits that worsened over time. Nerve conductions of the tail (caudal nerve)

was performed on a separate cohort of mutant (n=14) and WT littermates (n=13) every 4 weeks from 8 to 48 weeks. Mutant rats showed a progressively decline in the amplitude of the compound action potential after 20 weeks, whereas the amplitude progressively increased in their WT littermates. Separate cohorts of rats were sacrificed at 7, 40, and 48 weeks and analyzed by light microscopy. In mutant rats, there was a reduced density of myelinated axons and active axonal degeneration in distal but not proximal nerves, and in the fasciculus gracilis of the cervical spinal cord at 40 and 48 weeks. These findings were not present in the 7-week-old cohort of mutant rats, or in WT rats at 7 or 40 weeks. A genetically authentic animal model of CMT2A that develops a progressive, length-dependent axonal neuropathy will be a valuable tool for examining the pathogenesis and treatment of CMT2A.

THE ROLE OF IMMUNE CELLS IN NERVE DEGENERATION AND REGENERATION: A NEW PERSPECTIVE

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Traditionally the role of immune cells in nerve degeneration and regeneration has focused on the infiltration of inflammatory monocytes into the distal nerve after nerve injury and the phagocytosis by the resulting macrophages of myelin and axonal debris, thereby clearing a path for regenerating axons. Therefore, it was surprising when we discovered that in CCR2 knockout (KO) animals, in which the entry of these inflammatory monocytes does not occur, that Wallerian degeneration precedes normally. We now report that the reason for this is that neutrophils and Schwann cells compensate for the decrease in macrophage accumulation. Furthermore, nearly complete depletion of circulating neutrophils by systemic injection of an antibody to Ly6G leads to an inhibition of myelin clearance both in CCR2 KO and in wild type animals. On the other hand, we have demonstrated a second site of macrophage accumulation in wild type animals, namely around axotomized sensory neurons in dorsal root ganglia (DRGs). Blockade of that accumulation, for example as occurs in CCR2 KO animals, leads to a dramatic impairment of nerve regeneration. To examine the relationship between macrophages and regeneration further the monocyte chemokine CCL2 was overexpressed in DRG neurons in intact animals by viral infection using an AAV5 containing the CCL2 coding sequence. The resulting overexpression of CCL2 led to the accumulation of macrophages in DRGs even though no injury had taken place and subsequently to an increase in the intrinsic growth capacity of the sensory neurons. Examination of changes in gene expression in the DRGs in these animals revealed increased expression of the cytokine leukemia inhibitory factor and an increase in its downstream signaling pathway that involves the phosphorylation and nuclear translocation of STAT3. Strikingly, pharmacological blockade of STAT3 activation inhibited the increase in the neurons' growth capacity produced by the virus. These results reveal unexpected interactions between immune cells and neurons facilitating nerve degeneration and regeneration and could lead to therapies to improve regeneration after injury or in disease.

DIFFERENTIATION POEMS AND CIDP BY TERMINAL LATENCY INDEX

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We used terminal latency index (TLI) as a tool in differentiation between POEMS syndrome and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Comparison of median and ulnar nerve conduction studies including motor conduction velocity (MCV), distal motor latency (DML) and terminal latency index (TLI) were studied in 18 POEMS patients, 58 matched CIDP patients and 30 normal controls. In this cohort, the average age at evaluation was 51.56±8.77 years old in POEMS group and that of 58 CIDP patients was 46.34±16.38 years old. Except the ulnar terminal latency index in CIDP group, POEMS and CIDP patients demonstrated prolonged distal latencies, low conduction velocities and increased terminal latency indexes compared with the normal group. Reduced conduction velocities and higher terminal latency indexes in POEMS group than in CIDP group was found. Increased TLI was demonstrated in 55.6%(median nerve) and 52.9%(ulnar nerve) POEMS and that in CIDP patients was 25.9%(median nerve) and 22.4%(ulnar nerve). Decreased TLI was found in 24.1%(median) and 20.7%(ulnar) CIDP patients and none in POEMS. Temporal dispersion (TD) and conduction block (CB) were more often seen in CIDP patients with increased TLI than that in POEMS. Compared with CIDP and POEMS showed greater slowing of the intermediate nerve segments and relatively more uniform demyelination. About 25% CIDP demonstrated more distal conduction slowing and more TD and CB especially in those with increased TLI. Terminal latency index combined with TD and CB may be helpful in differentiating POEMS from CIDP.

THE AXONAL PROPERTIES IN PREDIABETIC PATIENTS

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The purpose of our study is to exam whether electrophysiology changes could be detected in prediabetes patients and to discover the possible mechanism of nerve injury in prediabetes stage. We analysis and compare the nerve excitability test data between prediabetic patients and age-matched normal control subjects. Prediabetes is defined by American diabetes association (ADA) as one of the three following: HbA1C 5.7% to 6.4%, fasting glucose 100mg/dL to 125mg/dL, and 2 hour oral glucose tolerance test 140 to 199 mg/dL. Patients with

radiculopathy, myelopathy, entrapment neuropathy such as carpel tunnel syndrome, and polyneuropathy were excluded. The strength-duration time constant (SDTC) and superexcitability showed significant difference ($p<0.05$) between two groups. We also find increased threshold electrotonus in depolarization (TEd) and reduced relative refractory period (RRP) and refractoriness in 2.5 msec. These early changes in prediabetic patient are similar in nerve excitability feature of diabetic patients. However, the above changes are not found in motor axonal excitability test. Our data supports that nerve excitability test may be a useful, non-invasive, and less time dependent tool to detect peripheral nerve injury in prediabetic stage. The sensory axons are more vulnerable than motor axons. Superexcitability is the most sensitive parameter in prediabetes.

TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY IN POLAND-GENOTYPIC AND CLINICAL PRESENTATION

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Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is an autosomal dominant disorder caused by mutations of TTR gene and is associated with variable penetrance. TTR-FAP is rare, except for endemic areas. This is a retrospective study of TTR-FAP patients diagnosed at our center between 1970-2016. We identified four families with different TTR mutations. In one family with V71A mutation, nine family members over four generations diagnosed with TTR-FAP was followed since 1970. In the other families the index cases with different mutations were identified between 2014-2016. Affected family members with V71A mutation developed severe progressive polyneuropathy with cachexia, with onset of the disease between ages 29 and 44. Three patients presented with marked visual symptoms (one patient underwent vitrectomy). Nine patients died 4 to 11 years after disease onset. Two patients (sisters) underwent liver transplantation – one died after 11 years of disease at age 40, second is 49 years old and wheelchair-bound as her symptoms continue to progress. The TTR mutations diagnosed in the index cases of three other families are: D38V, F33L and V30M. They all presented with similar clinical picture of late-onset TTR-FAP with predominant progressive axonal sensory, motor and autonomic polyneuropathy. All three index cases were men, the onset of symptoms was between 50-54 years with numbness and paresthesia in the feet followed by weakness and autonomic dysfunction. All had excessive weight loss resulting in cachexia and were diagnosed with cardiomyopathy. No patient suffered from visual symptoms. All three patients progressed to stage II of TTR-FAP – walking with assistance. Time to diagnosis was 3.5-5 years. Due to advanced stages of their disease these patients were not suitable for therapy with tafamidis or the liver transplantation. The TTR D38V (p.D58V) was confirmed as a *de novo* mutation, which is uncommon in TTR-FAP. In the remaining families carriers of TTR mutations were identified and are followed up. Pedigree analysis of the family with F33L mutation revealed affected members who with high probability died from TTR-FAP. Our study suggests that patients with TTR-FAP in Poland exhibits clinical and genetic heterogeneity.

THE GENE MUTATION OF CHINESE PROBANDS WITH CHARCOT-MARIE-TOOTH DISEASE

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Objective To identify the gene mutation of Chinese Charcot-Marie-Tooth pedigrees and investigate the correlation among the clinical manifestation, electrophysiology and mechanism of different genotype.
Methods We included 105 pedigrees with CMT enrolled in our hospital from January, 2007 to December 2013. We recorded clinical features, CMTNS and electrophysiological data at diagnosis. The patients underwent mutation analysis of PMP22, Cx32, MPZ, MFN2, HSPB1, HSPB8 using MLPA, DHPLC and Sanger gene sequencing.
Results We found 31 PMP22 duplication pedigrees (29.5%), 8 Cx32 pedigrees (7.6%), 4 MFN2 pedigrees (3.8%), 3 MPZ pedigrees (2.8%)
Conclusions : In Chinese Han population, the proportion of PMP22 duplication is relatively low, the majority of clinical manifestation is classical CMT. Axonal CMT can show isolated lower extremity injury, with central nervous system involvement. HMN may be an underestimated clinical types, the identification should be done with caution in differential diagnosis.

Key words : Charcot-Marie-Tooth, gene diagnosis, clinical phenotype

AUTONOMIC NERVE FIBER INVOLVEMENT IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting toxicity in the treatment of many cancers. Most CIPN studies preferentially focus on sensory fiber loss and dysfunction. Here, we compared the structural and functional recovery of autonomic fibers in sweat glands (sweat gland nerve fiber density, SGNFD) and

sensory fibers (intra-epidermal fiber density, IENFD) in mouse footpads after exposure to a maximum tolerated dose (MTD) of several common chemotherapy agents. Additionally, we assessed footpad sweat production as a functional correlate to SGNFD reductions. Female Balb-c mice (3-animals/group) were treated with a MTD of four anti-tubulin drugs: paclitaxel (PCA, 30 mg/kg), ixabepilone (IXA, 2 mg/kg), eribuline (ERIB, 1.2 mg/kg), vinoelbine (VINO, 11 mg/kg), or corresponding placebo given intravenously, MWF for two weeks. Recovery was assessed at 24-hours, 1, 2, 4, 8, 12 and 24 weeks following the last dose. Footpads were processed to visualize epidermal nerve fibers using PGP9.5 and autonomic nerve fibers with tyrosine hydroxylate and PGP9.5. Ixabepilone-treated mice experienced significant reductions in SGNFD at 24hrs, while IENFD nadir occurred at a later time point, 2-weeks. The recovery to baseline levels occurred more quickly for IENFD (4-weeks) than SGNFD (8-weeks). In contrast, Vinorelbine and Eribuline treated mice experienced a maximum deficit in SGNFD and IENFD at 24hrs and SGNFD recovery was slower (24-weeks) compared to IENFD (4-weeks). PCA-treated animals showed more severe IENFD and SGNFD deficits compared to the other agents with both IENFD and SGNFD not recovering completely until 24-months. Reductions in TH-SGNFD were comparable or more pronounced to decreases in PGP9.5-SGNFD for all agents and timepoints. PCA-treated animals demonstrated reductions in footpad sweat droplet number thereby providing a functional correlate. Together, these data indicate that in mouse models of CIPN, autonomic nerve fibers are affected more severely than sensory nerve fibers, and also recover more slowly than intraepidermal nerve fibers. Autonomic dysfunction may be an important and under-appreciated consequence of chemotherapy exposure.

SCHWANN CELL-SPECIFIC DELETION OF THE ENDOSOMAL PI 3-KINASE VPS34 LEADS TO DELAYED RADIAL SORTING OF AXONS, ARRESTED MYELINATION, AND ABNORMAL ERBB2-ERBB3 TYROSINE KINASE SIGNALING

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The PI 3-kinase Vps34 (Pik3c3) synthesizes phosphatidylinositol 3-phosphate (PI3P), a lipid critical for both endosomal membrane traffic and macroautophagy. Human genetics have implicated PI3P dysregulation, and endosomal trafficking in general, as a recurring cause of demyelinating Charcot-Marie-Tooth (CMT) peripheral neuropathy. Here, we investigated the role of Vps34, and PI3P, in mouse Schwann cells by selectively deleting *Vps34* in this cell type. *Vps34*-Schwann cell knockout (*Vps34*^{SCKO}) mice show severe hypomyelination in peripheral nerves. *Vps34*$^{-/-}$ Schwann cells interact abnormally with axons, and there is a delay in radial sorting, a process by which large axons are selected for myelination. Upon reaching the promyelinating stage, *Vps34*$^{-/-}$ Schwann cells are significantly impaired in the elaboration of myelin. Nerves from *Vps34*^{SCKO} mice contain elevated levels of the LC3 and p62 proteins, indicating impaired autophagy. However, in the light of recent demonstrations that autophagy is dispensable for myelination, it is unlikely that hypomyelination in *Vps34*^{SCKO} mice is caused by impaired autophagy. Endosomal membrane traffic is also disturbed in *Vps34*$^{-/-}$ Schwann cells. We investigated the activation of the ErbB2/3 receptor tyrosine kinases in *Vps34*^{SCKO} nerves, as these proteins, which play essential roles in Schwann cell myelination, are known to traffic though endosomes. In *Vps34*^{SCKO} nerves, ErbB3 was hyperphosphorylated on a tyrosine known to be phosphorylated in response to Nrg1 exposure. The overall level of ErbB2 was also decreased during myelination. Our findings suggest that the loss of Vps34 alters the trafficking of ErbB2/3 through endosomes. Abnormal ErbB2/3 signaling may contribute to the hypomyelination observed in *Vps34*^{SCKO} mice.

EVALUATION OF DERMAL NERVE FIBERS IN CIDP NODO-PARANODOPATHY PATIENTS

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The recent identification of IgG4 anti-neurofascin (Nfascin) antibodies in a group of patients has widened the spectrum of presentation for Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP). These patients can be distinguished by disabling tremor, poor response to intravenous immunoglobulin and distal and sensory disturbances. Cell-adhesion molecule Nfasc155 and CNTN1 are expressed on the Paranodal Junction (PNJ) of nodes of Ranvier, and play key roles on sodium channel clustering and glia-axon interactions. Quantification of unmyelinated intraepidermal nerve fibers (IENF) is a useful parameter employed in small nerve fiber pathology diagnosis. In addition the immunohistochemistry evaluation of dermal nerve fibers allows to examine morphological changes of myelin sheath and Ranvier nodes structure. We performed immunofluorescent colocalization studies using antibodies to visualize axons (Protein-gene-product 9.5, Neurofilament, Tubulin), sheath of myelin (Myelin-Basic-Protein) and specifically nodal/paranodal/juxtaparanodal structures (panNfascin, Nfascin155, Nfascin186, Caspr, CNTN1, potassium and sodium channels) in skin

tissues from seronegative and seropositive CIDP patients. We analyzed axon and myelin sheath damage, abnormal nodal-paranodal-juxtaparanodal architecture and morphometric parameter as internodal length of Ranvier nodes. Our results on skin biopsies from three IgG4 Nfasc155-positive CIDP patients revealed complete loss of Nfasc155 staining at the paranodes, asymmetrical paranodes and widening of the nodes of dermal myelinated nerve fibers. One IgG4 CNTN1-positive CIDP patient showed abnormal nodal/paranodal immunostaining with different features as compared with IgG4 Nfasc155-positive patients suggesting specific changes. However, such alterations were not found in four seronegative CIDP patients. Our data support the hypothesis that examining specific axonal and myelin markers could provide diagnostic and prognostic clues on nodo-paranodopathies. The goal of this study is attempt a possible correlation between the presence of serum autoantibodies and structural changes in nodal/paranodal regions of dermal nerve fibers in CIDP patients. Knowledge of autoantibodies expression in the peripheral myelinated nerves of CIDP patients could serve for stratifying patients and potentially guiding personalized treatments.

CHARCOT-MARIE-TOOTH DISEASE ASSOCIATED WITH DEAFNESS AND/OR SCOLIOSIS: NEW MUTATIONS DISCOVERED IN *SH3TC2* GENE

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Charcot-Marie-Tooth disease is one of the most frequent inherited peripheral neuropathies (1/2500). So far, mutations in more than 80 genes have been identified causing either the demyelinating form (type 1) or the axonal form (type 2). Duplication of PMP22 gene is the most frequent cause of autosomal dominant demyelinating form. Autosomal recessive demyelinating form is often due to SH3TC2 gene mutations. Patients suffer then from early severe neuropathy starting in the first decade. Scoliosis and deafness are often observed. We analysed 200 patients suffering from peripheral neuropathy, by multiplex-ligation-dependant-probe-amplification (MLPA), followed by targeted next-generation-sequencing (NGS) using a 92-gene custom panel designed for the diagnosis of Charcot-Marie-Tooth and associated neuropathies. Mutations of interest were verified by Sanger sequencing. Diagnosis was positive for 114 patients. As expected, the most frequent mutation was the PMP22 duplication detected in 30 patients. Deletion of PMP22 was observed in 18 patients and pathogenic point mutations were detected in 66 patients. SH3TC2 gene appeared to be the most frequently mutated with nine patients diagnosed. Associated with known mutations, four new mutations have been identified: two nonsense mutations and two missense mutations. All these patients presented deafness and/or scoliosis. SH3TC2 appears to be an important gene involved in Charcot-Marie-Tooth disease, often associated with deafness and /or scoliosis. It is important to pay attention to these associated symptoms in Charcot-Marie-Tooth patients in order to guide their diagnosis and to improve their medical care.

AUTOSOMAL RECESSIVE *MME* MUTATIONS BROADEN THE CLINICAL PHENOTYPE ASSOCIATED WITH CMT2T

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MME (*membrane metalloendopeptidase)* mutations, inherited in an autosomal recessive fashion, have been recently identified in 10 Japanese probands (Higuchi et al. 2016). Thus, *MME* has been included in the list of CMT genes as a new autosomal recessive axonal form, CMT2T (MIM 617017), and moreover, it is considered a strong candidate for the genetic diagnosis of unsolved late-onset CMT2 cases. In fact, few months later Auer-Grumbach et al. (2016) reported 19 European probands with autosomal dominant late-onset CMT2 and mutations in *MME*. We have investigated a clinical series of 190 patients diagnosed of motor or sensory-motor peripheral neuropathy using an updated version of our custom gene panel, which includes *MME*. In this study, we report 6 probands with CMT2, intermediate CMT or dHMN/CMT2 and homozygous or compound heterozygous mutations in *MME*, and 1 proband with

CMT1 and a heterozygous mutation in *MME*. We have identified 7 different type of mutations: 1 novel splice donor variant, 1 frameshift, 2 nonsense and 3 missense mutations. The two nonsense changes, p.Trp24* and p.Arg448*, and the splice donor variant c.196+1G>A, were detected in homozygous or compound heterozygous state in 3 patients, while the frameshift mutation, p.Pro156Leufs*14, was detected in homozygous or heterozygous in the remaining 3 patients. Strikingly, the two nonsense and the frameshift mutations had been previously reported as causative for autosomal-dominant CMT2T (Auer-Grumbach et al. 2016). Out of three missense mutations, one is novel (p.His712Tyr), and two are reported in control databases (p.Asn689Lys and p.Arg748Trp). This study shows that the autosomal recessive CMT2T is common in Spanish population, and moreover, it suggests that screening of *MME* using gene panel testing could help to improve diagnosis of unclarified inherited peripheral neuropathies cases.

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MOLECULAR DIAGNOSIS OF INHERITED PERIPHERAL NEUROPATHIES: GENE PANEL VS. EXOME SEQUENCING

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Inherited peripheral neuropathies (IPNs) encompass a group of disorders highly heterogeneous, clinically and genetically. Charcot-Marie-Tooth (CMT) disease is closely related to distal hereditary motor neuropathy (dHMN) or distal spinal muscular atrophy (DSMA), and some patients show additional signs associated with amyotrophic lateral sclerosis (ALS). Targeted gene panel and exome sequencing are considered to be powerful and cost-effective tools for diagnosis of these disorders. We have investigated a clinical series of 226 patients diagnosed of motor or sensory-motor peripheral neuropathy: 24 families were investigated by exome sequencing and, 202 cases were tested using different updated versions of a gene panel (Neuro-104, Neuro-111, and Neuro-119). Each version comprises 104, 111 or 119 IPN genes, respectively and it shows a high coverage performance: percentage of analyzable target base with >20 coverage was 99,99%. Both exome and gene panel capture libraries were based on SureSelect capture technologies (Agilent Technologies), and sequencing was performed in MiSeq or HiSeq Illumina equipment. We have identified novel genes and novel mutations in known genes, broadening the phenotypical spectrum associated with IPNs. Exome sequencing has allowed us to identify causative gene in 58% of familiar or sporadic cases: *MORC2*, *AARS, BSCL2, KIF1A, GARS, EGR2, FIG4, DNAJB2, DRP2, IGHMBP2, DAO, SOD1, FIG4*. Gene panel testing has been mostly performed in sporadic cases, and it has allowed us to identify either disease-causing or candidate mutations in 40% of cases: *KIF1A* and *BICD2* were the most common genes mutated. Update gene panels Neuro 111 and Neuro119 have revealed novel mutations in genes recently associated to CMT2 and CMT1 disease: *MME* and *PMP2*, respectively. In sum, both strategies have helped us to achieve a more accurate clinical and genetic reclassification of these disorders, an impossible challenge using conventional sequencing methods. Our study expands the clinical phenotype previously associated to known IPN causing-gene, and emphasizes that gene panels should be considered as a first diagnosis method for unclarified IPN patients.

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UPDATING THE CLASSIFICATION OF CMT AND RELATED NEUROPATHIES. RESULTS OF AN INTERNATIONAL SURVEY

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Charcot-Marie-Tooth (CMT) disease is a hereditary neuropathy with a relatively homogeneous phenotype but is genetically heterogeneous. Moreover, nerve conduction studies distinguish different forms, adding another level of complexity. The current classification of CMT being difficult to understand for physicians, scientists and patients, we presented and published a proposal for updating this classification, based on inheritance, nerve conduction findings and gene/mutation involved. Inputs from colleagues prompted us to conduct a survey in order to try to reach some consensus about our proposals.
We conducted an internet survey between October and December 2016. The link to complete the survey was sent several times by email with an introduction to more than 300 people. Participants were contacted

through the emailing list from the last CMT meeting in Venice (September 2016) and additional physicians and scientists who are involved in CMT care and research were contacted as well.
One hundred seven people from various countries (mainly France, Italy and the USA) answered the survey. Most (81%) of the participants were between 30 and 60 years of age, 60% being physicians and 37% being scientists. The vast majority (65%) considered the proposal constituted an improvement over the historical classification whereas 23% wanted to keep the old one. About the order of information, 39% of participants thought the mode of inheritance should come first, whereas 33% felt the phenotype should be placed at the beginning. Ninety-one percent of people thought CMT should be kept as a generic name for hereditary sensory and motor neuropathy. For pure sensory neuropathy, 48% favoured HSN over HSAN although 41% thought the opposite and 80% of participants felt dHMN should be kept for distal motor neuropathy. About nerve conduction findings, 70% of participants thought the intermediate phenotype has to be kept and 68% favoured our proposal to replace "1" by "de" (for demyelinating) and "2" by "ax" (for axonal). Finally, 88% of responders thought that genetic information should be included in the classification of CMT.
Overall, our proposal of a new classification received a very good appreciation from physicians and scientists implicated in the care of patients with hereditary neuropathy.

HEMOLYTIC SIDE EFFECTS OF IVIG: MODELING PREDICTS RISK REDUCTION WITH ANTI-A/B IMMUNOAFFINITY CHROMATOGRAPHY AND TO A LESSER EXTEND WITH ANTI-A DONOR SCREENING.

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The risk of hemolytic events (HEs) with intravenous immunoglobulin (IVIG) therapy appears to be linked to the isoagglutinin (anti-A and anti-B) level of the specific IVIG product. Using published anti-A and anti-B titers for seven IVIG products and corresponding HE rates reported to the EudraVigilance database, we developed a mathematical model to predict the risk of HE to patients receiving IVIG products of given anti-A and anti-B levels. Modeling was performed separately for the risk to patients with blood groups A, B, AB and O and the overall population risk was estimated assuming a blood group distribution of 42% A, 10% B, 4% AB and 44% O. Applying the prediction model, we calculated the HE risk for an IVIG product produced via a chromatographic process (Privigen®, CSL Behring) a) without any isoagglutinin reduction measures (2007–2013), b) with an anti-A donor screening program eliminating approximately 5% of donors with high anti-A titers (2013–2015), c) incorporating an anti-A/anti-B specific immunoaffinity chromatography (IAC, IgIsoLo™) step in the manufacturing process (since 2016) and d) with both measures (b and c) combined; as well as for an IVIG product produced with a Cohn-like cold ethanol fractionation process (Carimune® NF/Sandoglobulin®, CSL Behring). Isoagglutinin titers in IVIG products, measured by European Pharmacopoeia direct assay, were provided by Dr C Bellac, SwissMedic, Bern, Switzerland. The predicted risk was highest with the chromatographically purified IVIG without isoagglutinin reduction (1.87 cases expected per 1000 kg IVIG used). Anti-A donor screening reduced the predicted risk to 0.78 cases/1000 kg. A greater risk reduction was predicted with the IAC isoagglutinin reduction step (0.11 cases/1000 kg). The combination of both methods produced little benefit (0.09 cases/1000 kg) versus IAC alone. The predicted hemolytic risk with IVIG produced by Cohn-like ethanol fractionation was low (0.09 cases/1000 kg). An observational cohort study to confirm these hemolytic risk reductions is in progress. At present, the observed hemolytic risk for anti-A donor screening appears consistent with the prediction calculated by the model; results for IAC isoagglutinin reduction are expected in 2019.

SENSITIVITY OF THE CMT INFANT SCALE: PRELIMINARY ANALYSIS OF CMT SUBTYPES AND COMPARISON TO CONTROLS

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The CMT Infant Scale (CMTInfS) is an outcome measure of functional ability for young infants and children aged <5 years. CMTInfS aligns with the CMT Pediatric Scale and CMT Neuropathy Score to measure disease severity across the lifespan. To measure gross motor and fine motor function, CMTInfS comprises of two subscales: 16 gross motor (e.g. head control, crawling, walking, jumping and hopping) and 15 fine motor function items (e.g. grasping, reaching, tearing paper and buttoning). Overall and subscale-specific function is expressed

as a z-score based on normative reference values (positive z-scores indicate poorer function). A total of 109 controls aged 0-58 months (mean age 22, SD 15m) have been assessed across Australia (n=75), Thailand (n=33) and USA (n=1). Total CMTInfS z-scores did not differ significantly between sites (Australia vs Thailand) (p=0.293) or gender (p=0.126). Data collection is ongoing and infants aged <5 years are eligible for inclusion. To date, 17 infants (53% male) aged 8-58 months (mean age 36, SD 16m) with a range of CMT subtypes (13 CMT1A, 1 CMT1D, 1 CMT4C, 1CMT X3 and 1 unidentified gene) have been assessed with CMTInfS. Mean total z-score for infants with CMT (1.5, SD 2.4, range: -0.9 – 8.0) was significantly higher than controls (0.0, SD 1.0, range: -2.0 – 3.6, t=-2.50, p=0.023). Differences between affected infants and controls were larger in infants older than 12 months. Infants with CMT1A (CMTInfS z-score 0.8, SD 1.6) and CMT4C (z-score 0.1) were less affected than CMTX3 (z-score 3.5) and CMT1D (z-score 8.0). The gross motor function subscale differed significantly between CMT cases and controls (2.4, SD 3.8 vs 0.0, SD 1.0; p=.019) and a significant difference was also observed for the fine motor function subscale (0.7, SD 1.5 vs 0.0, SD 1.0; p=0.009). Reliability, Factor and Rasch analysis of the CMTInfS is underway to assess validity. Initial results support the sensitivity of CMTInfS in distinguishing between infants with and without CMT. Preliminary analyses also suggest the scale is sensitive to genetic subtype. With increased power, CMTInfS promises to become a useful outcome measure of disease severity and function in infants with CMT.

ANTI-NFASC155 IGG4 AFFECT PARANODE STRUCTURE IN ANIMAL MODELS

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Contactin-1, contactin-associated-protein-1 (Caspr1), and neurofascin-155 (Nfasc155) are essential for the formation of paranodal axoglial junctions. IgG4 autoantibodies to contactin-1, Caspr1, and Nfasc155 are associated with subsets of patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) presenting with common clinical features. Anti-contactin-1 IgG4 autoantibodies have been shown to be pathogenic and to affect the paranodal axoglial junctions *in vivo* and i*n vitro*. By contrast, the pathogenic effect of anti-Nfasc155 IgG4 have not been demonstrated. Here, we purified anti-Nfasc155 IgG4 from CIDP patients' plasma and investigated their effects after passive transfer. To determine whether these antibodies can pass the paranodal barrier, we performed intraneural injections of anti-Nfasc155 IgG4 autoantibody. By contrast to anti-contactin-1 IgG4, anti-Nfasc155 did not penetrate the paranodal regions after intraneural injections, but bound to the surface of the Schwann cell. To perform chronic exposure, Lewis rats were implanted with intrathecal catheter and anti-Nfasc155 IgG4 were administrated in a daily manner during three weeks. IgG4 to Nfasc155, but not control IgG4, induced progressive clinical deteriorations characterized by gait ataxia and hindlimb paraparesis. These deteriorations were associated with nerve activity loss in motor spinal nerves and with a selective loss of the paranodal specialization characterized by the disappearance of the Caspr1/contactin-1/Nfasc155 complex at paranodes. The passive transfer of anti-Nfasc155 IgG4 thus seem to induce similar pathogenic effects as the anti-contactin-1 IgG4. However, the pathogenic mechanisms leading to paranode disappearance appear different. Our findings indicate that IgG4 directed against Nfasc155 are pathogenic and further show that these antibodies are reliable biomarkers of a specific subset of CIDP patients.

ENHANCEMENTS TO THE RARE DISEASES CLINICAL RESEARCH NETWORK CONTACT REGISTRY FOR THE INHERITED NEUROPATHIES CONSORTIUM

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The Rare Diseases Clinical Research Network (RDCRN) Contact Registry for the Inherited Neuropathies Consortium (INC) is an interactive online platform that empowers patients with inherited neuropathies and their family members by providing relevant information about clinical studies being conducted by INC investigators, enabling them to participate in online studies, and facilitating communication and interaction with the inherited neuropathies community. As of February 12, 2017, over 2,700 individuals enrolled in the RDCRN INC Contact Registry, including patients with CMT1A, CMT2A, CMT1B, CMT4, CMTX, patients with multiple, other or unknown CMT disease types, and unaffected family members of patients with CMT. The RDCRN INC Contact Registrants and their participation in RDCRN INC Contact Registry studies to date have proven essential to the Inherited Neuropathies Consortium, and have resulted in completed protocols, publications and the development of Patient-Reported Outcome Measures (PROMs) currently being investigated within INC clinical sites. These results have made a large contribution towards the goal of improving care for people with inherited neuropathies. Recently, several enhancements have been made to the RDCRN INC Contact Registry to better fit the needs of the consortium and improve patient experience. These enhancements include creating mobile friendly webpages, updating enrollment form content, access to a customized dashboard, and the ability of registrants to explore their data in comparison to other registrants. We will review these enhancements in depth, and demonstrate their impact on the growth and development of the RDCRN INC Contact Registry.

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(NINDS). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

ANTI-A DONOR SCREENING AND THE RISK OF HEMOLYTIC ANEMIA WITH HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN TREATMENT – A HOSPITAL-BASED COHORT STUDY IN THE US

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Hemolytic anemia (HA) is a complication of intravenous immunoglobulin (IVIG) treatment, particularly in patients receiving high dose IVIG for immune modulation, such as Guillain-Barré syndrome or chronic inflammatory demyelinating polyneuropathy. The primary mechanism for the increased risk is believed to be passive acquisition of anti-blood group A and B antibodies (isoagglutinins) from the IVIG product. To reduce the quantity of isoagglutinins, an anti-A donor screening was implemented for the IVIG Privigen® from 2013–15 and donors with high titers were excluded from contribution to pooled plasma. Anti-A donor screening was replaced since 2015 with an immunoaffinity chromatography step, which decreases isoagglutinins to a greater extent, but no data are available to test its clinical effectiveness. To test the effectiveness of the donor screening, two cohorts of patients treated with Privigen® before and after start of donor screening were identified from a hospital-based administrative database of 862 US hospitals with in- and outpatient discharge diagnoses, procedures, drug utilization and laboratory tests between 1/2008 and 12/2012 (period 1) and between 10/2013 and 12/2015 (period 2). Privigen® dose per kg body weight was estimated from the daily quantity administered and age- and sex-specific US population body weight estimates. HA within 30 days of Privigen® use was assessed from manual records review and the incidence rate of HA in the two periods compared. Incidence rate ratios (IRR) of HA were adjusted for sex, age, treatment setting, indication and dose per kg body weight using period 1 as reference. The incidence rate of HA was 1.05/10,000 person-days (95% confidence interval: 0.82–1.34) in period 1 (68 HAs in 644,756 person-days) and 0.82 (0.58–1.12) in period 2 (39 HAs in 476,931 person-days). The adjusted IRR was 0.82 (0.55–1.23). Significantly less HA risk was found with high dose (≥1.75 g/kg body weight) Privigen®, IRR 0.48 (0.22–1.04, p=0.03). We conclude that anti-A donor screening and exclusion of donors with high anti-A titers from plasma pools is associated with a decreased risk of HA with IVIG.

CLONICAL SYMPTOMS OF SUBACUTE MYELO-OPTICO NEUROPATHY ARE ELOCITED BY MYELOPATHY RATHER THAN PERIPHERAL NEUROPATHY

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Subacute myelo-optico neuropathy (SMON) is the intoxication of clinoquinol with main clinical symptoms of paresthesia and spasticity of legs. These symptoms have been considered to be elicited by the disturbance of spinal cord and peripheral nerve as the intoxication of clinoquinol. However, as to the patients with SMON who have been still living after the onset of disease, the examination of nerve conduction velocities are in normal ranges and the clinical symptoms of peripheral neuropathy are not observed now. In order to investigate whether the peripheral neuropathy were observed in the early stage of SMON, We investigated the longtidunal changes of electrophysiological results in 4 patients who could examine the nerve conduction studies from early stage of SMON until the present time. As to the disturbance of pyramidal tract functions (myelopathy) in SMON patients, the central motor conduction times were calculated by transmagnetic stimulation of motor cortex, cervical roots and lumbar roots. The peripheral nerve conduction velocities of sensory nerve were examined with the sural nerves. As the results, in 4 patients with SMON who could examine the electrophysiological examination from the early stages of SMON until 20 to 27 years later, the central motor conduction times of leg muscles from motor cortex to lumbar roots were prolonged in the SMON patients compared to the normal cases. These results suggest the presence of disturbances of conduction velocities of spinal cord. Conduction velocities of sensory nerve velicities (SNCVs) showed the delayed SNCVs of sural nerves(24-33m/sec) at the first examination from the onset of 2-5 years. However from 20 to 27 years later, SNCVs of these cases were covered to35-42m/sec. From these electrophysilogical examinations, it was suggested that the presenting main symptoms of SMON were the disturbance of myelopathy, and the disturbance of peripheral nerve function had been recovered after onset of SMON being elapsed a long time,

CAN NK CELLS HELP DISCRIMINATE IVIG TREATMENT RESPONSE IN PATIENTS WITH CIDP?

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Natural Killer (NK) cells are part of our innate immune system with regulatory and effector functions. They comprise the first line of defence in the recognition and destruction of virus-infected and pathologically altered cells.

Different studies suggest that the treatment with intravenous immunoglobulins (IVIg) has an immunomodulatory effect on NK cells. IVIg is a first-line treatment for various autoimmune diseases in particular in chronic inflammatory demyelinating polyneuropathy (CIDP). The lack of a predictive marker for IVIg responsiveness in CIDP avoids the early preservation of non-responding patients.
To better understand the effect of IVIg in patients with CIDP, we tested whether IVIg treatment altered the NK cell status. Additionally, we analysed if the alteration in the populations may serve as a surrogate marker in predicting the outcome of IVIg treatment. Using semi-quantitative PCR and flow cytometry in the peripheral blood of patients with CIDP, we analysed the effects of IVIg on the NK cell population before treatment initiation and 24h after first dose and correlated the changes with the reponsiveness to IVIg.
IVIg administrations induced a reduction in the expression of several typical NK cell genes. Interestingly, this IVIg-induced reduction of NK cells was reversible four weeks after the IVIg treatment. Flow cytometry data revealed that IVIg reduced the cytotoxic CD56dim NK cell population, while regulatory CD56bright NK cells remained almost unaffected or were even increased. Interestingly, we found that the observed effects on NK cells almost exclusively occurred in CIDP patients who responded to IVIg therapy.
Correlation between the changes in the NK cell population and treatment efficiency suggests a crucial role for NK cells in the immunomodulatory mechanism of IVIg. Further studies are warranted to investigate whether the differences in the NK cell status of patients with CIDP represent a reliable surrogate marker in predicting the outcome of IVIg therapy.

PATHOGENESIS OF CHARCOT-MARIE-TOOTH DISEASE TYPE 2C DUE TO MUTATIONS IN TRPV4

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Mutations in transient receptor potential vanilloid (TRPV4), a calcium-permeable non-selective ion channel, cause Charcot-Marie-Tooth disease type 2C (CMT2C). TRPV4 is unique in that it represents the only membrane-expressed ion channel in CMT and thus a potential therapeutic target. Previous work has suggested that TRPV4 mutations lead to gain of channel function and toxicity in cultured cells. Neuropathy-causing mutations of TRPV4 largely cluster in the cytosolic ankyrin repeat domain (ARD) that is known to mediate protein-protein interactions, suggesting that pathogenesis may be related to disruption of such interactions. In order to identify TRPV4-interacting proteins, we performed two unbiased proteomics screens and identified multiple cytoskeletal-modifying proteins including syndapin-1, a neuronal protein known to promote axonal outgrowth by influencing the actin cytoskeleton. In cultured cells, we have shown that TRPV4 and syndapin-1 co-localize to highly dynamic actin-rich cellular processes and together stimulate robust neurite extension, but this facilitation of neuritogenesis is impaired by disease-causing mutations in TRPV4. We have also shown that over-expression of syndapin reduces TRPV4-mediated calcium influx in cultured cells and rescues toxicity of mutant TRPV4. In addition, syndapin over-expression suppresses mutant TRPV4 phenotypes in a *Drosophila* model of TRPV4-related neuropathy. Further, we have demonstrated that treatment of *Drosophila* with a specific TRPV4 channel antagonist ameliorates TRPV4 mutant toxicity. Together, our data highlight the importance of TRPV4 interaction with cytoskeletal proteins such as syndapin-1 in the pathogenesis of CMT2C. Specifically, our results suggest that mutations in TRPV4 disrupt the normal role of TRPV4 in regulation of cytoskeletal dynamics and that interactions with the cytoskeleton reciprocally modulate TRPV4 channel function and influence toxicity of mutant TRPV4.

ANTI-GM1 ANTIBODY MEDIATED MODELS OF AXONAL AND DEMYELINATING GBS IN GLYCOSYLTRANSFERASE-MODIFIED TRANSGENIC MICE.

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Guillain-Barré syndrome (GBS) is in part mediated by anti-GM1 ganglioside antibodies induced by preceding infections. Anti-GM1 antibodies target plasma membrane GM1 that is extensively distributed in both glial and axonal membranes, particularly at the node of Ranvier. Antibodies deposited at this site in models of GBS are associated with complement deposition, conduction block, structural disruption of ion channels and macrophage infiltration. The wide distribution of the GM1 ganglioside target leads to unwanted complexity in ascribing pathological outcomes to injury of cell-specific membranes, in particular unravelling the consequence of paranodal Schwann cell membrane injury on axonal function, and vice versa. To overcome this impasse, we have generated transgenic mice through glycosyltransferase manipulation that express GM1 exclusively in neurons or glia, thus allowing us to very specifically target and injure axonal or glial membranes with a single anti-GM1 ganglioside antibody. Through this route we can create mouse models of both the axonal and demyelinating forms of GBS, induced by a single anti-GM1 antibody, thus creating otherwise highly comparable conditions. Here, we show anti-GM1 antibody binding is restricted to the nodal axolemma in GalNAcT$^{-/-}$-*Tg(neuronal)* mice and conversely to paranodal loops in GalNAcT$^{-/-}$-*Tg(glial)* mice. When anti-GM1 antibody and a source of complement is added to a nerve-muscle *ex vivo* injury paradigm, there is a loss of axonal integrity (i.e. loss of neurofilament immunolabeling) when the neuronal membrane is targeted in GalNAcT$^{-/-}$-*Tg(neuronal)*. Conversely, axonal integrity is maintained when the paranodal membranes are decorated by antibody and

complement products *ex vivo* in GalNAcT$^{-/-}$-*Tg(glial)* mice. In a passive immunisation model *in vivo*, GalNAcT$^{-/-}$-*Tg(neuronal)* mice acutely develop weakness, respiratory dysfunction, associated complement deposition, and degenerative pathology in distal axons. In contrast, GalNAcT$^{-/-}$-*Tg(glial)* mice have significantly fewer abnormalities under the same acute conditions. These data indicate the high vulnerability of axonal membranes to acute injury and underline the importance of developing specific axonal protection strategies. In summary, targeting the nodal axolemmal or glial membranes allows us to study associated nodal pathology, and determine the downstream consequences on function and axon fate, currently a major area in GBS clinical research.

TERMINAL LATENCY INDEX (TLI) AND SENSORY ELECTROPHYSIOLOGY IN PARAPROTEINEMIC CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP).

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Objective: To differentiate sensory electrophysiology, TLI and treatment response in patients with paraproteinemic CIDP.
Background: Low TLI has been reported as a useful electrophysiological marker for MAG-CIDP. To our knowledge comparison of sensory electrophysiology and TLI of paraproteinemic CIDP subgroups have not been previously reported.
Methods: Retrospective review(January 2000-December 2015) of 89 patients with CIDP fulfilling electrophysiological criteria(AAN ad hoc subcommittee and Albers and colleagues).CIDP patients with diabetes(n=18) were excluded. 71 patients were divided into idiopathic (n=40) and paraproteinemic CIDP(n=31). Paraproteinemic CIDP sub-groups**:** MAG(8), non-MAG(8) and IgG(15) were compared to idiopathic CIDP(40). These groups were compared for demographics, history of cancer, CSF protein, sensory conductions, TLI measurements and response to treatment using chi-square tests for binary and categorical variables and t-tests for continuous measures.
Results: There was a higher proportion of females in idiopathic-CIDP compared to non-MAG-CIDP (50% vs 13%). Idiopathic group having a higher proportion of patients on monotherapy(59% vs 50%) and combination therapy(38% vs 17%) compared to non-MAG. Higher mean CSF protein compared to MAG-CIDP(p=0.001) was seen in the idiopathic. The difference between idiopathic and IgG-CIDP was significant for overall Rx response(p=0.025) and Rx response in patients with follow-up(p=0.01). For both variables, patients in the idiopathic group had a higher proportion of patients on combination therapy and lower proportion of no treatment offered compared to patients in the IgG-CIDP. 50% of non-MAG-CIDP patients had a history of cancer vs 0% of MAG-CIDP. None of the other differences were significant. There were no group differences in sensory electrophysiology and TLI.
Conclusions: Sensory electrophysiology and TLI may have no value in differentiating paraproteinemic CIDP. CSF protein is higher in idiopathic CIDP compared to MAG-CIDP. Idiopathic-CIDP has a higher proportion of females compared to non-MAG-CIDP and a higher proportion of patients on combination therapy compared to IgG-CIDP. Cancer screening should be considered in patients with non-MAG-CIDP.

DOES ELECTROPHYSIOLOGY AND TREATMENT RESPONSE DIFFER IN IDIOPATHIC VS DIABETIC CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)?

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INTRODUCTION: Sensory electrophysiology and Terminal latency index (TLI) differences have been described in various CIDP sub-groups.
OBJECTIVE: Evaluate electrophysiology, TLI and treatment response in idiopathic and diabetic CIDP.
METHODS: Retrospective review of 147 patients with CIDP who underwent electrodiagnostic evaluation (January 2000-December 2015). 89 patients fulfilled electrophysiological criteria described by Ad hoc subcommittee of American Academy of Neurology (AAN) and Albers et al. We excluded patients(31) with acute inflammatory demyelinating neuropathy, hereditary sensorimotor neuropathy, vasculitis and polyneuropathy with paraproteinemia.
58 patients were divided into idiopathic(40) and diabetic(18) groups. These groups were compared for age, sex, history of cancer, CSF protein, response to treatment, sensory response abnormalities and TLI measurements using chi-square tests for binary and categorical variables and t-tests for continuous measures. All testing was at the alpha=0.05 level.
RESULTS:
Group differences for age, sex, history of cancer, CSF protein and treatment response were not significant. Comparing TLI values in measurable responses, the difference between the two groups for tibial TLI was significant (p=0.012), with idiopathic group having a lower mean as compared to the diabetic. TLI values differences for median, ulnar and peroneal nerves were not significant. The difference in abnormal rates of sensory responses was significant for the sural nerve with the idiopathic group having a lower rate compared to the diabetic group (80% vs 100%, p<0.05). No differences were noted for the ulnar, median and radial nerves.
CONCLUSION:
Tibial TLI and sural sensory responses have some value in differentiating the two groups. Larger prospective studies are needed to confirm our findings.

INTRAVENOUS IMMUNOGLOBULIN (IVIG) FOR RESTABILIZATION TREATMENT AFTER IVIG WITHDRAWAL IN CHRONIC

INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP). RESULTS FROM THE PRE-RANDOMIZATION PHASE OF THE PATH STUDY

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IVIg is an important treatment option for CIDP. Although recommended by treatment guidelines, little is known about the consequences of temporary IVIg withdrawal to assess ongoing immunoglobulin need. PATH is a randomized, double-blind trial of the subcutaneous immunoglobulin (SCIg) IgPro20 (Hizentra®, CSL Behring) in CIDP. Before SCIg randomization, subjects underwent periods of IVIg withdrawal (12 weeks or until pre-determined indications of clinical deterioration) and IVIg restabilization (IgPro10; Privigen®, CSL Behring). Subjects not showing deterioration during withdrawal period were withdrawn from study. To proceed to SCIg randomization, subjects had to achieve “CIDP stability” (no relevant change in INCAT score at last two restabilization visits and at least the same total score as at screening). 245 subjects entered the IVIg withdrawal period. 208 (85%) of these qualified for IgPro10 restabilization; 28 subjects (11%) were not IVIg dependent, and 9 (4%) were withdrawn for other reasons. One subject withdrew consent before IgPro10 dosing. At the end of the IgPro10 restabilization period, CIDP stability was achieved in 83% of subjects (22 did not reach stability, 13 were withdrawn for other reasons). Post-study follow-up information was available for 16/22 subjects who did not reach stability: 9 (56%) had improved to baseline clinical status and 7 had not, meaning at least 87% of the subjects improved to their pre-study status. During the restabilization period, 188/207 subjects (91%) improved in at least one of the predefined outcome measures. On average, subjects improved by 1.2 points in INCAT total score, 5.7 points in I-RODS centile score, 12 kPa in mean grip strength (dominant hand), and 3.6 points in MRC sum score. Improvement occurred with a median of 23 days after the first IgPro10 dose in one or more efficacy outcome measures and in 99% of cases after the third IgPro10 maintenance infusion. Headache and nasopharyngitis were the most frequently reported adverse events (AEs) during restabilization. AEs deemed causally related were mostly mild or moderate. No unexpected AEs or laboratory or vital sign findings associated with IgPro10 occurred during the study. In summary, IgPro10 reversed neuromuscular disability and improved activity/participation after previous clinical deterioration during an IVIg withdrawal period.

IS PMP22 DUPLICATION THE ONLY COPY NUMBER VARIATION (CNV) RESPONSIBLE FOR CHARCOT-MARIE-TOOTH DISEASE? NEW CNV DISCOVERED USING COV’COP

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PMP22 duplication is the most frequent cause of Charcot-Marie-Tooth disease (CMT). Since it discovery, more than 80 genes have been identified to be potentially responsible for CMT disease. However only Single Nucleotide Variations (SNVs) or small indels have been described. This could be due to the new sequencing strategy (NGS), especially NGS by amplicon sequencing, for whose few convenient tools are available and easily usable to detect CNVs responsible for inherited disease. To overcome this problem, we designed “Cov’Cop”, a user-friendly tool able to detect CNVs among amplicons sequencing data. Using the run‘s coverage file provided by the sequencer, “Cov’Cop” simultaneously analyzes all the patients of the run using a two-stages algorithm containing correction and normalization levels and provides an easily understandable output, showing with various colors, potentially deleted and duplicated amplicons. We validated our method on several datasets, including those of our targeted NGS panel screening 89 genes known to be involved in CMT and close pathologies. Cov’Cop detected easily PMP22 duplication and deletion in our patients, confirmed by MLPA. In addition, Cov’Cop permitted the detection of new CNVs different from the PMP22 duplication, in CMT patients. We confirmed these CNVs by quantitative PCR and CGH array. We present here one of these CNVs: the duplication of *AARS* gene detected in CMT patients and we discuss the pathogenicity of this new CNV. Additional CNVs responsible for CMT disease are probably still to be discovered and we believe that Cov’Cop will help molecular geneticists to rapidly identify them.

THALIDOMIDE THERAPY FOR POEMS SYNDROME: A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL WITH LONG-TERM EXTENSION STUDY

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POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome is a rare cause of demyelinating neuropathy associated with plasma cell dyscraisia and vascular endotherial (VEGF) overproduction. Although number of therapeutic interventions for plasma cell dysorders have been applied to POEMS syndrome, there have been no randomized clinical trials. This phase 2/3 double blind, randomized, placebo comtrolled trial was performed to investigate the safety and efficacy of thalidomide for patients with POEMS syndrome who are not eligible for stem-cell transplantation. The primary endpoint was the reduction rate of serum VEGF concentrations at 24 weeks in intention to treat analysis. Additional outcomes of long-term extension study included progression-free survival. Twenty-five POEMS patients were randomly assigned to either thalidomide plus dexamethasone or placebo plus dexamethasone from Nov 11, 2010, to July 3, 2014. one patient in the placebo group was excluded from analyses because of a protocol violation. The adjusted mean serum VEGF reduction rate at 24 weeks was 0.39 (SD, 0.34) in the thalidomide group compared with -0.02 (0.54) in the placebo group (p=0.04). The Kaplan-Meier rate of progression-free survival at 12 months was 0.77 in the thalidomide group, as compared with 0.50 in the placebo group (HR, 0.373 ; 95% CI, 0.080 to 1.343). In the randomized study period, mild sinus bradycardia was more frequent in the thalidomide group than in the placebo group (54% vs 0%; p=0.006). Thalidomide suppresses serum VEGF concentrations and lengthened pregression-free survival in POEMS patients who are ineligible for stem cell transplantation. Although thalidomide treatment has a risk of bradycardia, the benefits would exceed the risk. This study is registered with the UMIN Clinical Trials Registry, UMIN000004179.

A NEW SYT2 MUTATION CAUSING PRESYNAPTIC NEUROMUSCULAR JUNCTION DYSFUNCTION AND DISTAL MOTOR NEUROPATHY (LEMS-CMT)

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Autosomal dominant mutations in Synaptotagmin-2 (SYT2), a synaptic vesicle protein that functions as a calcium sensor for neurotransmission, have been previously linked to presynaptic neuromuscular junction (NMJ) dysfunction and motor neuropathy in two families. Both pathogenic mutations (Asp307Ala and Pro308Leu**)** were located in the C2B domain of SYT2, which is essential for neurotransmitter release at the NMJs. We report a family with a new missense mutation in the C2B domain of SYT2 and a similar phenotype characterized by a slowly progressive, predominantly motor neuropathy and evidence of presynaptic NMJ dysfunction on nerve conduction studies. The index case is a 50 year-old woman with gradually progressive weakness of her extremities. She had normal developmental milestones, but was found to have bilateral high arched feet and hammertoes and occasional falls around the age of 8. She gradually developed progressive leg weakness, worsening bilateral hand cramping, weak handgrip, and only mild paresthesias on distal extremities. Family history is remarkable for similar symptoms reported by her maternal grandfather, two maternal uncles, her mother and a younger sister. Her neurological exam revealed inability to walk on heels or toes, significant distal lower extremity weakness and absent ankle deep tendon reflexes. Cranial nerve examination and coordination were normal and there were only non-specific sensory changes in the lower extremities. EMG/NCS revealed normal sensory responses throughout; however, motor nerve evaluation demonstrated globally reduced amplitudes with a >200% increment after brief isometric contraction. Further electrophysiological evaluation with slow (3Hz) repetitive nerve stimulation of the right ulnar motor nerve revealed a 40% decremental response in amplitude and a >200% increase in amplitude immediately after a one-minute period of sustained muscle contraction, which rapidly extinguished after one minute. Voltage-gated calcium channel (VGCC) antibodies and a chest CT were normal. Targeted Sanger sequencing revealed an Ile371Lys mutation in SYT2, which is located in the C2B domain and is predicted to impair protein function. SYT2-related neuropathy is a rare disease, but should be suspected in patients presenting with a combination of pre-synaptic NMJ dysfunction (resembling Lambert-Eaton myasthenic syndrome) and a predominantly motor neuropathy, especially in the context of a positive family history.

PRELIMINARY RESULTS FOR CHARCOT-MARIE-TOOTH PATIENT-REPORTED SURVEY

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Charcot-Marie-Tooth (CMT) disease affects roughly 1 in 2,500 individuals and is described as an inherited peripheral neuropathy primarily affecting distal muscles. Limited studies detail patient-reported impact of muscle weakness on functional activities. This anonymous survey was developed with input from clinical experts and patient interviews and aimed to better understand the prevalence and impact of various CMT clinical manifestations on patients' lives. The survey was administered online to the Hereditary Neuropathy Foundation's (HNF) patient contact database and is ongoing through June 2017. Here we present preliminary data on patient characteristics and disease impact for 626 CMT patients collected February 17–21, 2017. Respondents were mostly female (61%) and mostly from the US (74%). Median age (range) at symptom onset was 14 years (0-84 years), at diagnosis was 36 years (2-83 years), and at present was 55 years (6-89 years). The sample was representative of all CMT types (CMT1,2,3,4,and X). The most common physical and clinical manifestations of CMT were problems with balance (87%), ankle weakness/foot drop (81%), loss of feeling or abnormal sensation in the lower leg/foot (81%), and hand muscle weakness (78%). Maintaining balance, walking long distances, and climbing up and down stairs were key challenges associated with ankle weakness/foot drop. Foot drop was considered by 72% to be the primary factor contributing to falls, which averaged 2.5 falls to ground per month. Of those with foot drop, 86% had bilateral weakness. A majority of respondents (76%) used some form of assistive device for mobility, including ankle-foot orthotics/below-the-knee leg braces (40%), canes/walking sticks (34%), and custom foot orthotics/inserts (26%). The most common drug therapy included pain and anti-inflammatory medications (41%). Foot surgery was the most common surgical procedure received (24%) and toe surgery was the most common surgery considered (23%). Key symptoms that affected quality-of-life "very much" included problems with balance (65%), ankle weakness (foot drop) (62%), and fatigue (49%). These data suggest a high prevalence of lower leg muscle weakness; therefore, therapies aimed at improving ankle weakness and the resulting foot drop and imbalance may be beneficial to patients' daily functioning and quality of life.

CRITICAL FACTORS AFFECTING FUNCTIONAL RECOVERY AFTER PERIPHERAL NERVE INJURY

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Nerve fiber regeneration and complete functional recovery after peripheral nerve injury do not always occur and can be influenced by many factors including patient age, gender, lesion site, injury severity, size of the gap between damaged nerve stumps and time interval that elapses before performing surgical repair.
The poor outcome occurring after a long delay can be due to loss of the neuron ability to regenerate, loss of the Schwann cell ability to support regeneration and, of course, progressive muscle atrophy.
The aim of this study was to investigate the nerve regeneration after delayed repair and to study the degenerative processes of the denervated distal nerve stump and denervated muscle. In particular, the analyses were focused on the role of NRG/ErbB system, that is expressed both in nerve and in muscle tissue, during degenerating and regenerating processes.
Functional recovery analysis performed after nerve repair showed that only the group repaired immediately and not the groups repaired with a delay of 3 or 6 months, recovered partially. Nevertheless, morphological analyses demonstrated that, despite the delay, the nerve fibers are still able to regenerate, even if they are fewer and smaller than the immediate repaired group. Moreover, the analysis of the NRG1/ErbB system showed a significant decrease of soluble NRG1 in both degenerating and delayed-repaired nerves. The poor outcome after delayed nerve regeneration might be explained by Schwann cell impairment and the consequent ineffective support for nerve regeneration.
As regards denervated muscle analysis, results showed that ErbB receptors expression is related to the innervated state of the muscle, with an upregulation of ErbB2 clearly associated with denervation state. Interestingly, NRG1 isoforms are differently regulated depending on the type of nerve injury.
Future experiments will be needed to address the in vivo efficacy of different isoforms of NRG1 both in injured nerve and denervated muscle.

AEROBIC EXERCISE FOR SUBJECTS AFFECTED BY CHARCOT MARIE TOOTH (CMT) NEUROPATHY: RESULTS OF A MULTICENTER, PROSPECTIVE, RANDOMIZED, SINGLE BLIND, CONTROLLED CLINICAL TRIAL

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We planned a multicenter, prospective, randomized, single blind, controlled study to evaluate the efficacy and safety of an innovative rehabilitation protocol based on the use of treadmill training in a CMT1A population.
The protocol required that subjects were blindly randomized into two treatment groups, SPE (three months of respiratory, proprioceptive and stretching exercises) or TreSPE (the same treatment plus aerobic training at the treadmill). Subjects were evaluated at baseline (T0), after three month of treatment (T1) and further three months of follow up free of therapy (T2). The full assessment included: 6-MWT (primary outcome measure), 10-MWT, Walk-12, Short physical performance battery (SPPB); lower limbs dynamometric strength evaluation; Berg Balance scale (BBS); CMT neuropathy score; Medical Outcomes Study Short Form 36 (SF36).
A total of 53 subjects (mean age of 52.1±11.9 years) were recruited. At T1 we found a significant improvement in both groups in the 6-MWT ($p<0.05$), 10-MWT ($p<0.05$), BBS ($p<0.05$) and SPPB ($p<0.01$), while at T2 only the 6-MWT was still significantly improved ($p<0.05$) in the SPE group. No significant differences between groups were observed for any of the outcome measures. Performances on Walk 12 did not significantly change during follow-up ($p=0.27$). Concerning the SF36, we did not observe consistent changes during follow-up or consistent differences comparing the two treatments.
In conclusion, this multicenter, prospective, randomized, single blind, controlled study shows that the combination of respiratory, proprioceptive and stretching exercises has a positive impact on the performance of CMT patients, especially regarding walking tests. The aerobic exercise at the treadmill, is well tolerated but apparently does not add any further improvement to the conventional treatment. We speculate that the relatively low clinical severity of the patients, due to the selection criteria, may have prevented a positive effect of treadmill exercise.

SEMI-AUTOMATED MUSCLE MRI-VOLUMETRY FOR MYOPATHY AND NEUROPATHY PATIENTS

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Muscle MRI is increasingly used in neuromuscular patients to detect changes in muscle volume, muscle fat infiltration and edema. Muscle MRI are mostly analyzed by qualitative means as quantitative analysis is time-consuming and not well established. Here, we developed a novel method for semi-automated segmentation of muscle MRI data sets. Based on axial T1-weighted Dixon MRI stacks, muscle volumes were quantified by an adapted water-shed algorithm. Muscle volumes of thighs and calves were determined separately and the ratio of thigh/calf was calculated. 24 myopathy, 8 neuropathy patients and 28 healthy controls were included in the study. Muscle volumes determined by semi-automated segmentation were very similar to manually segmented data sets, differences being <2%. This was the case for patients as well as healthy controls. The time-saving effect of automated segmentation was very strong (400 vs 30 min. per patient). Muscle volumes of the thigh and also of the calf of myopathy patients showed a highly significant difference ($p<0.001$) compared to healthy subjects. In neuropathy patients there was a just significant difference ($p<0.05$) of muscle volumes compared to healthy patients that did not sustain in Bonferroni's Multiple Comparison Test. The ratio of thigh/calf muscle volume was significantly different comparing patients with myopathy and neuropathy ($p<0.05$). Subgroup analyses of different groups of myopathy patients showed highly significant differences ($p<0.001$) in myositis, limb-girdle-muscular dystrophy and metabolic myopathy, compared to healthy patients, but no significant differences in-between these groups. Taken together, the data shows that automated segmentation of muscle MRI allows for exact and fast quantification of muscle volumes in neuromuscular patients. Higher patient numbers are necessary to test differences between specific disease groups. Further studies should also address the possible use as a marker of disease progress for clinical studies or therapy monitoring.

CLINICAL AND PATHOLOGICAL FINDINGS IN FAMILIAL AMYLOIDOTIC POLYNEUROPATHY DUE TO TRANSTHYRETIN E61K

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Familial amyloidotic polyneuropathy (FAP) is an autosomal dominant hereditary systemic amyloidosis caused by mutation of transthyretin (TTR) gene, and usually shows sensory dominant polyneuropathy and autonomic neuropathy at the initial stage. The pathogenesis of neuropathy is not well understood, and explained by several mechanisms, including such as mechanical compression, vessel occlusion, TTR toxicity and Schwann cell dysfunction. We describe a sporadic patient with late-onset FAP due to TTR E61K. She noticed dysesthesia first in the foot at age 70. The symptoms were slowly progressive, and abnormal sensations were extended up to the both upper arms and the both knees at age 76. Distal muscle weakness and atrophy was also observed in the extremities. She noticed difficulties in walking and frequent diarrhea. Echocardiogram revealed diffuse left ventricular hypertrophy, suggesting cardiac amyloidosis. Amyloid deposits were not detected in the endoneurim or perineurium of the sural nerve 7 years after the onset of the disease, but a marked loss of myelinaed and unmyelinated nerve fibers was observed in it. TTR-derived amyloid deposits were confirmed in the peroneous brevis muscle, salivary gland and heart tissue. DNA analysis revealed the heterozygote mutation, p.E81K (E61K)/c.241G>A, of TTR gene, and she was diagnosis as FAP. These findings suggest that the proximal parts of peripheral nervous system might be strongly involved by TTR aggregates or amyloid fibrils. Blood-nerve barrier in

the distal part of peripheral nerves could be preserved until later in the patient. Several biopsy sites other than nerve may be helpful and necessary for diagnosis of TTR amyloidosis in mild or late-onset FAP as our case.

AXONAL CMT WITH ATYPICAL PROXIMAL WEAKNESS CAUSED BY TRANSLATIONAL ELONGATION OF THE 3' UTR IN *NEFH*

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Mutations in *NEFH* gene encoding the heavy neurofilament protein are usually associated with neuronal damage and susceptibility to amyotrophic lateral sclerosis (ALS). Recently, frameshift variants in *NEFH* (p.Asp1004Glnfs*58 and p.Pro1008Alafs*56) have been reported to be the underlying cause of the axonal CMT (CMT2CC). The frameshift mutation resulted in stop loss and translation of a cryptic amyloidgenic element (CAE) encoded by the 3' UTR. This study also identified a *de novo* c.3015_3027dup frameshift mutation predicting p.Lys1010Glnfs*56 in *NEFH* from a CMT2 family with atypical clinical symptom of proximal dominant weakness. This mutation is located near the previously reported frameshift mutations, suggesting a mutational hot spot. These relatively frequent deletion/duplication events with this resign might be caused by the putative hairpin structure. Patient's lower limb MRI revealed a marked hyperintense signal changes in the hip muscles than those in the thigh or lower leg muscles. This study also observed an anticipation pattern of earlier onset (12 yrs old for mother to 6 yrs old for daughter) and more severe symptoms in later generation. Therefore, this study suggests that the stop loss and translational elongations by the 3' UTR of the *NEFH* mutations may be relatively a frequent genetic cause of axonal peripheral neuropathy with the specific characteristics of proximal dominant weakness and an anticipation pattern.

DO ANTI-MAG TITERS HAVE A GOOD CORRELATION WITH CLINICAL STATUS IN IgM ANTI-MAG NEUROPATHY?

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The myelin-associated glycoprotein (MAG) is a transmembrane glycoprotein localized in periaxonal Shwann cells and oligodendroglial membranes of myelin sheaths. MAG contains a carbohydrate epitope (HNK-1) that is a target antigen in autoimmune peripheral neuropathy associated with monoclonal IgM gammopathy. In these neuropathies, numerous studies report the absence of correlation between the titers of anti-MAG antibodies and the disease course. Anti-MAG titers and IgM level at diagnosis are not always associated with disease severity and there is not good correlation between pre- and post- treatment anti-MAG titers in patients who respond clinically to immunomodulators. MAG belongs to siglec-4a family and the linkage of sialic acid to the underlying sugars is an important determinant of siglec binding. MAG shows high affinity for alpha- 2,3-linked sialic acid (2,3-SA).Moreover, human monoclonal IgM possesses 5 heavy chain glycosylation sites at Asn 171, 332, 395, 402 and 563 with sialylated olidgosaccharides and high-mannose type oligosaccharides. IgM may bind to MAG via these glycan epitopes as an alternative and additional route of antigen binding other than through the Fab V regions. This MAG-Glycans IgM interaction may be clinically neutral but could lead to an overvaluation of the biological results. In this study, we analyzed 8 sera from patients with IgM reactivity against MAG: 7 of them had an anti-MAG neuropathy with various degrees of severity, and the last one had IgM monoclonal gammopathy, strong serum anti-MAG reactivity but no neurological disease. IgM were extracted and purified from these sera by affinity chromatography. For each batch, an aliquot was digested by Jack bean alpha-mannosidase and anti-MAG reactivity was performed by ELISA and indirect immunofluorescence (IIF), before and after demannosylation. These extracts, tested in an iso quantitative way with regard to the original serum, showed a decrease of activity (ELISA) and intensity (IIF) after demannosylation. Furthermore, ELISA anti-MAG was carried out in 49 sera from patients with IgM monoclonal gammopathy without neurological impairment: 6 of them (12.2%) showed a significant biological response. Taking into account the fact that anti-MAG antibodies are pathogenic (in animals models), these results support the hypothesis of neutral intermolecular interactions between IgM and MAG.

THE RELATIONSHIP BETWEEN CENTRAL AORTIC SYSTOLIC PRESSURE AND PERIPHERAL BLOOD PRESSURE IN PATIENTS WITH POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME

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Recent developments have validated non-invasive means of measuring central arterial blood pressure (CASP) and have shown that CASP and peripheral blood pressure (pBP) are unidentical entities. Patients with postural orthostatic tachycardia syndrome (POTs) have marked tachycardia with no associated decrease in pBP. We asked if the reflex tachycardia, which corresponds to postural dizziness in these patients, could be a result of a decrease in

CASP. Two male patients, 19 and 21 years of age, with clinical features typical of POTs went through a complete battery of autonomic screening tests. The sympathetic and parasympathetic responses were normal other than a heart rate increase of 31 and 41 beats per minute, respectively, on standing. There was no significant decrease or increase in pBP on standing for 2 and 5 minutes. CASP was measured non-invasively by a device Bpro^{R} that imputes the measured radial waveform onto the brachial blood pressure to generate a pressure waveform from which a numerical CASP value is derived. The CASP measurements for both patients did not decrease on standing for 2 and 5 minutes. Our preliminary observation suggests that the basis of tachycardia in POTs patients may not be a decrease in central blood pressure. We are proceeding to systematically study more POTs patients to corroborate the above observation. We are also trying to compare the difference between pBP and CASP in POTs and age, gender-matched normal controls. The major limitation of the study is the model-based mathematical derivation, rather than direct measurement, of CASP. We are proceeding to systematically study more POTs patients to corroborate the above findings.

THE RELATIONSHIP BETWEEN CENTRAL AORTIC SYSTOLIC PRESSURE, PERIPHERAL BLOOD PRESSURE AND SYMPTOMATIC IN PATIENTS WITH AUTONOMIC DYSFUNCTION

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Recent developments have validated non-invasive means of measuring central arterial blood pressure (CASP) and have shown that CASP and peripheral blood pressure (pBP) are unidentical entities. Orthostatic hypotension (OH) is a prominent component of autonomic dysfunction (AD), the consequent hypoperfusion of vital organs responsible for considerable morbidity and mortality. These structures are exposed to CASP rather than pBP. We sought to understand the relationship of CASP to peripheral blood pressure (pBP) in patients with autonomic dysfunction exposed to orthostatic stress. We reviewed autonomic function tests of patients tested at our laboratory over a 3-year period. The patients were divided into 5 cohorts: (1) no AD and no OH (2) no AD, with OH (3) mixed AD (4) parasympathetic dysfunction (5) sympathetic dysfunction. CASP was measured non-invasively by a device, Bpro^{R}, that imputes the measured radial waveform onto the brachial blood pressure to generate a pressure-wave form from which a numerical CASP value is derived. The difference and ratio of CASP to pBP was recorded at rest and after 2 minutes of standing. Out of 361 patients 168 had complete data and a definitive final diagnosis. Cohorts 1-5 had 74, 48, 15, 18, 13 patients respectively. Mean CASP-pBP difference in cohorts 1- 5 were -10.55, -11.02, -11.59, -13.44, -8.69 respectively at 0 minutes, and -13.52, -13.15, -13.18, -10.11, -8.46 respectively at 2 minutes. Mean CASP/pBP ratio in cohorts 1-5 were 0.91, 1.08, 0.92, 0.91, 0.93, 0.93 respectively at 0 minutes, and 0.89, 0.90, 0.89, 0.92, 0.92 respectively at 2 minutes. There was no significant difference in the response of CASP and pBP to orthostatic stress across abnormal cohorts 2 to 5 and in comparison with the "normal" cohort 1(p=0.268 to 0.983). There was also no relationship to symptoms, namely postural dizziness. In conclusion, autonomic dysfunction does not seem to affect the CASP-pBP relationship as measured by non-invasive means. The absence of true normal controls, the exclusion of significant number of patients because of incomplete data and the model-based mathematical derivation rather than direct measurement of CASP are limitations that we aim to address in follow-on studies.

AFTERDISCHARGES FOLLOWING M WAVES IN PATIENTS WITH VOLTAGE-GATED POTASSIUM CHANNELS ANTIBODIES

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We aimed to explore the correlation between afterdischarges in motor nerve conduction studies and clinical motor hyperexcitability in patients with voltage-gated potassium channels (VGKC) antibodies. Six patients with positive serum antibodies to contactin-associated protein-like 2 (CASPR2) or/and leucine-rich glioma-inactivated protein 1 (LGI1) were recruited, including 5 with autoimmune encephalitis, and 1 with cramp-fasciculation syndrome. Electromyography (EMG), nerve conduction studies (NCS) and F waves were performed, and afterdischarges were assessed. One patient was followed up. Five patients had clinical evidence of peripheral motor nerve hyperexcitability (myokymia or cramp), and four of them had abnormal spontaneous firing in concentric needle electromyography. Prolonged afterdischarges following normal M waves were present in all six patients, including the two patients who had no EMG evidence of peripheral nerve hyperexcitability (PNH). In the patient who was followed up, afterdischarges disappeared after treatment with intravenous immunoglobulin (IVIG). Afterdischarges in motor nerve conduction study might be more sensitive than needle electromyography for detecting peripheral motor nerve hyperexcitability in patients with VGKC antibodies, and could disappear gradually in accordance with clinical improvement and reduction of antibodies.

MUTIPLE SITES NERVE ULTRASOUND OF CHARCOT-MARIE-TOOTH TYPE 1A AND CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

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In our research, multiple sites measurement of cross sectional areas (CSA) by ultrasound was performed to differentiate Charcot-Marie-Tooth type 1A (CMT1A) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Twenty-eight patients with CIDP, 9 patients with CMT1A, and 14 healthy controls (HC) were recruited prospectively. Consecutive ultrasonography scanning was performed from wrist to axilla on median and ulnar nerves. CSAs were measured at 10 predetermined sites of each nerve. CMT1A had significantly larger CSAs at all sites of median and ulnar nerves (all $P<0.01$). In CMT1A, CSAs increased gradually and homogeneously from distal to proximal along the nerve, except potential entrapment sites. CIDP displayed three different morphological patterns, including mild enlargement in 15 patients, prominent segmental enlargement in 12, and slight enlargement in one, among which different treatment responses were observed. All patients with mild nerve enlargement treated with intravenous immunoglobulin (IVIG) were responsive (7/7), while less than half of those with prominent segmental enlargement (3/7) were responsive ($p<0.01$). The patterns of CSA enlargement were different in CMT1A and CIDP patients. Consecutive scan along the nerve and multiple sites measurement by ultrasound could supply more detailed morphological feature of the nerve and help to differentiate CIDP from CMT1A.

THE VALUE OF ELECTROPHYSIOLOGICAL TYPING AND CONDUCTION BLOCK FOR PREDICTION OF FUNCTIONAL OUTCOME IN GUILLAIN-BARRE SYNDROME

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Guillain-Barre syndrome (GBS) mainly consists of acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN). In AMAN, conduction block (CB) could be reversible or followed by axonal degeneration. We aimed to identify the correlation between existence of CB and the functional outcome for patients with GBS. 52 GBS patients were prospectively recruited for serial electrophysiological tests and disability evaluation. All patients received treatment of intravenous immunoglobulin (IVIG), and their disabilities were evaluated on the Hughes functional grading scale before and 1 month after treatment. Patients were classified into AIDP, AMAN, equivocal or normal according to electrodiagnostic criteria described by Rajabally *et al*. AMAN patients who had follow-up nerve conduction studies were further classified into three groups. Group 1 was typical AMAN without conduction block, group 2 had reversible conduction block, group 3 had conduction block and subsequential axon degeneration. Electrophysiological study results showed 20 AIDP, 24 AMAN, 7 equivocal and 1 normal. Probable or definite conduction block was observed in 11 AIDP patients and 16 AMAN patients. AMAN with CB had higher reduction of Hughes grade at one month (1.71±0.83 vs 0.43±0.79, $p=0.003$), and lower percentage of patients with slow recovery (unable to walk independently at six months) (7% vs 57%, $p=0.025$) compared with AMAN without CB. There were no significant differences between AIDP with CB and without CB, in the reduction of Hughes grade at one month. Among the 13 AMAN patients who were followed up, 4 were typical AMAN without CB (type1), 7 had reversible CB (type 2), 2 had CB and subsequential axon degeneration (type 3). Hughes grades at nadir were similar, while patients with reversible CB (type 2) had the largest Hughes Grade reduction at one month (type 2-2.14 vs type 1-0.25 vs type 3-1.5). None of the patients with axon degeneration (type1) showed rapid recovery, while 86% of those with reversible CB (type 2) had rapid recovery (improvement by two or more Hughes grades within four weeks after onset). Electrodiagnosis of AMAN with conduction block, especially reversible conduction block, might be a marker of good recovery.

FOLLOW-UP STUDY OF NERVE ULTRASOUND IN A PATIENT WITH PRIMARY NEUROLYMPHOMATOSIS

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We report a follow-up study of nerve ultrasound in a patient with primary neurolymphomatosis. A 54-year-old female presented with 5-months history of asymmetric limb pain, paresthesia, and weakness. Electrodiagnostic studies and spinal cord MRI showed an axonal neuropathy involving cervical and lumbosacral root, brachial plexus and left median nerve. Detection of malignant B lymphocytes by cytology and flow cytometry of cerebral spinal fluid confirmed the diagnosis of B-cell non-Hodgkin lymphoma. Nerve ultrasound showed dramatic enlargement of upper, middle and lower trunks of left brachial plexus (cross sectional area-CSAs 21 mm^2, 30 mm^2, 26 mm^2 respectively), middle trunk of right brachial plexus (CSA 15 mm^2), and proximal part of left median nerve (CSA 15-18 mm^2). Five months later, after five chemotherapy of rituximab and high-dose methotrexate, and intrathecal injection of cytosine arabinoside and dexamethasone, the patient had clinical improvement. Nerve ultrasound also showed alleviation of nerve enlargement. The CSAs of upper, middle and lower trunks of left brachial plexus were 5 mm^2, 14 mm^2, 14 mm^2 respectively; the CSA of middle trunk of right brachial plexus was 11 mm^2; the CSA of proximal part of left median nerve was 12-13 mm^2. Peripheral nerve ultrasound could help locate the distribution of nerve involvement, and reveals disease progression.

IENF AND MC ARE EARLY MARKERS OF PERIPHERAL INVOLVEMENT IN PD AND ARE DIFFERENTLY AFFECTED BY LDOPA TREATMENT

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A peripheral nerve involvement has been demonstrated in PD with the evidence of a small fiber pathology as possible intrinsic feature of the disease and a higher occurrence of large fiber neuropathy in patients longtime treated with L-Dopa. However the role that disease itself and Ldopa have on small and large fiber pathology in PD is still debated. We studied morphology and function of cutaneous innervation, in 85 idiopathic PD patients (49 male, aged 60.7±10.9), including 47 Naïve and 38 L-Dopa treated subjects without electrophysiological signs of neuropathy, with the aim to assess and characterize small and large fiber involvement and the effect of L-Dopa on it. All patients underwent a screening to rule out potentially neurotoxic conditions such as glucose intolerance, dysendocrinopathies, Vitamin E, B12 and folic acid deficiency, hepatic or renal failure, HIV or connective tissue disorders. Skin biopsies were obtained from thigh, leg and fingertip from the more affected side and bilaterally from thigh and leg in 35 patients. Samples were processed with indirect immunofluorescence technique using primary antibodies to mark different sensory and autonomic fiber populations. Density of intrapapillary myelinated endings (IME), Meissner's corpuscles (MC) and epidermal nerve fibers (ENFs) was obtained as well as a semi-quantitative assessment of sudomotor, pilomotor and vasomotor innervation. Further evaluation included sympathetic skin response, quantitative sensory testing and dynamic sweat test. Morphological and functional findings were compared with data extracted from our age and sex stratified normative dataset. IENF, IME, MC densities were lower ($p<0.01$) compared to controls in both naïve and L-dopa treated patients without differences between them except for MC density that was lower in L-dopa treated subjects (8.7±5.6 vs 14.5±8.9/mm2). A loss of autonomic nerves was also found in both groups compared to controls. Significant abnormalities ($p<0.01$) of thermal sensory thresholds, tactile thresholds, mechanical pain perception and reduced sweating output were present and similar in both groups. Our work confirms in PD an intrinsic peripheral nerve pathology involving both small and large fibers. Small fiber pathology isn't affected by L-Dopa treatment while sensory large fibers involvement, already present in naïve patients worsens with Ldopa treatment.

THE FOREARM/UPPER ARM RATIOS OF CROSS-SECTIONAL AREA ADD THE DIAGNOSTIC VALUE IN AMYOTROPHIC LATERAL SCLEROSIS

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The diagnosis of amyotrophic lateral sclerosis (ALS), a progressive, fatal neurodegenerative disorder defined by combined upper and lower motor neuron involvement, remains clinically based. The purpose of this study was to determine the ultrasound appearance of peripheral nerves in ALS patients, and to investigate whether parameters such as distal/proximal ratios of nerve cross-sectional areas (CSAs) may effectively differentiate disease mimics from ALS. Nerve ultrasound of the median, ulnar, and tibial nerves was performed in 53 ALS patients compared to 32 mimic patients (23 patients with peripheral nerve hyperexcitability syndromes (PNHS) and 9 patients with multifocal motor neuropathy (MMN)). Comparison of nerve and the distal/proximal ratios was undertaken by ultrasound and compared across clinical and neurophysiological parameters.Compared to normal controls, CSA of the median nerve at the upper arm was decreased in ALS ($p <0.001$). In comparison to ALS mimic disorders, CSA at the proximal site of the median, ulnar and tibial nerve and the forearm/upper arm ratio of the median and ulnar nerves had diagnostic values. In addition to CSA of the median, ulnar, and tibial nerves, the median and ulnar nerve forearm/upper ratios may provide a useful marker in for the diagnosis of ALS.

THE EFFECTS OF A PHYSICAL THERAPY PROGRAM ON BALANCE, MOBILITY, AND QULAITY OF LIFE IN PATIENTS WITH CHARCOT MARIE TOOTH PERIPHERAL NEUROPATHY: A RETROSPECITVE REPORT.

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Approximately 1 in 2,500 individuals are diagnosed with Charcot MarieTooth (CMT) disease, making it the most common hereditary peripheral neuropathy. There is no documented cure for CMT, however, many of those affected, report difficulty with mobility, imbalance, and weakness of the feet and hands. In the general population, patients reporting difficulty walking, falls and/or fear of falling, and poor strength are often referred to physical (PT) and occupational therapists (OT) to skillfully address the impairments and help restore function and quality of life (QOL). For patients diagnosed with CMT this is unfortunately not the norm, often leaving patients without any skilled guidance on managing their functional impairments.
11 patients (6 males) with a mean age of 52.27 years (27-74), went through a progressive and skilled PT intervention over the course of 3 months. The program included: therapeutic activities and exercise, neuromuscular reeducation, and manual techniques

to address the documented deficits. Patients were progressed through the program based on the Borg Scale. Each patient was assessed prior to and post the commencement of the program with the Berg Balance Scale, 6 Minute Walk Test, Timed Up and Go, Sit To Stand in 30 seconds, 20 Foot Self Selected and Fast Gait Speed, the Lower Extremity Functional Scale, Activities Balance Confidence form, Upper Extremity Functional Index, Oswestry, and the SF-36 QOL measure. The patients were seen by the same skilled PT 2-3 a week for 12 weeks. All but 2 patients improved in all measures taken, indicating an improvement in function and overall quality of life. Participants reported a total of 8 falls in the 3 months prior to the initiation of the study and only 1 fall was reported during the 3 month PT intervention.
This study makes a strong case for the utilization of skilled PT to address deficits in patients with CMT. Additionally, the utilization of objective, valid and reliable outcome measures in this population may help healthcare practitioners establish baseline function and response to change. A large randomized control trial is recommended to study the effects of a specific PT intervention on outcome measures in patients with CMT.

CLINICO-ELECTROPHYSIOLOGICAL CORRELATION WITH ANTI-NEUROFASCIN155 ANTIBODY LEVELS IN THE ANTIBODY-POSITIVE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY PATIENTS

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Clinical features of chronic inflammatory demyelinating polyneuropathy (CIDP) patients with autoantibodies against neurofascin (NF)155, one of the paranodal proteins, have been elucidated while the relation between anti-NF155 antibody levels and long-term clinical course in these patients still remains elusive. We retrospectively collected clinical, electrophysiological and immunological data of three anti-NF155 antibody-positive CIDP patients. They were all males and their ages at onset were 16, 26, and 34 years old. Their clinical severity was evaluated by deep tendon reflexes (DTRs), grip strength and Hughes functional scale. Anti-NF155 antibody levels were measured by flow cytometry using HEK293 cell lines stably expressing human NF155. After immunotherapies of various combinations, including intravenous immunoglobulin, plasmapheresis, corticosteroids and other immunosuppressants, were introduced, their clinical parameters were gradually improved. Decreased or absent DTRs were normalized and grip strength was increased by more than 10 kg. Hughes functional scale scores were decreased by at least one point compared with those at nadir. NCS findings of all three patients also showed obvious amelioration. For example, their F wave latencies in the right ulnar nerve were improved from 63 to 38 ms, from 48 to 35 ms, and from 64 to 38 ms, respectively. Anti-NF155 antibody levels after treatment were decreased in two patients whose pre- and posttreatment sera were available. When dose of oral prednisolone was being tapered, they experienced re-exacerbation of clinical parameters, especially DTRs and grip strength. Their NCS findings and serum anti-NF155 antibody levels were also deteriorated. Exacerbation of these laboratory data in one patient preceded his clinical fluctuation, which suggests that NCS and serum anti-NF155 antibody levels could be used as early disease activity markers. In this case series, not only clinical but also laboratory data support a notion that anti-NF155 antibody-positive CIDP patients were reactive to combined immunotherapies including corticosteroids. Even though various treatments were administered to them, efficacy of oral corticosteroids seemed to be dose-dependent. Optimal disease activity markers and immunotherapies for long-term maintenance of remission in anti-NF155 antibody-positive CIDP should be identified.

evaluated by deep tendon reflexes (DTRs), grip strength and Hughes functional scale,
After starting immunotherapies,

THE CHALLENGES OF ACCURATE DIAGNOSIS OF ZIKA VIRUS ASSOCIATED GUILLAIN-BARRÉ SYNDROME (GBS) IN A DENGUE ENDEMIC AREA.

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Singapore's Zika virus (ZIKV) outbreak started in late August 2016. Over a period of 2 months, we studied 8 patients enrolled into our institution's prospective Guillain-Barré syndrome (GBS) database for relationship to ZIKV infection. We also studied 3 GBS controls that were seen before the established outbreak and 3 non-GBS controls. The 8 index cases tested negative for ZIKV PCR in blood and urine. We proceeded to test ZIKV IgG, IgM, dengue virus (DENV) IgG and IgM, and neutralization assays against ZIKV and DENV. One patient with anti- GQ1b IgG positive Miller Fisher syndrome had detectable ZIKV IgM and ZIKV IgG. The serum showed low titre DENV IgM and DENV IgG. Follow–up serum at about 2 months showed increase in ZIKV IgG. We believe this patient has ZIKV-GBS. One patient with acute motor sensory axonal neuropathy and another with acute inflammatory demyelinating polyneuropathy had high ZIKV IgM but low DENV IgM and IgG. Another patient with MFS showed high levels of ZIKV and DENV IgM but low IgG. The latter two patients had GBS before the ZIKV outbreak in Singapore. We suspect these 3 patients could have ZIKV-GBS, but are awaiting convalescent sera for confirmation. Two patients seen during the outbreak had detectable levels of ZIKV IgG but serial testing showed a decline after a period of 2-3 months. The initial and follow-up sera showed raised DENV IgM and IgG levels in one and raised IgG levels in the other. In addition, both had stronger neutralizing capacity against DENV

than ZIKV suggesting that the initially detectable ZIKV IgG levels was due to cross reactivity with previous DENV infection. Four patients, 1 GBS control and 2 non-GBS controls also showed serological response consistent with previous exposure to DENV. One normal control showed nil exposure to both viruses. In summary, using various overlapping serological methods we diagnosed 1 definite and 3 suspect ZIKV GBS cases. Our findings highlight 1) Insensitivity of blood and urine PCR to diagnose ZIKV-GBS 2) The problems of interpreting ZIKV serology from cross-reaction with DENV 3) Serial serology increases diagnostic accuracy.

VECTOR-BORNE VIRAL INFECTIONS IN GUILLAIN BARRE SYNDROME PATIENTS

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Guillain-Barré syndrome (GBS) is an acute monophasic immune-mediated polyradiculoneuropathy. It is believed that acute inflammatory demyelinating poliradiculoneuropathy is caused by T-cell mediated autoimmune response targeting peripheral nerve myelin. Molecular mimicry plays a role in the pathogenesis of some GBS cases. This mechanism has been well demonstrated in the acute motor axonal neuropathy (AMAN) variant, in which autoantibodies to Camphylobacter jejuni share epitopes with peripheral nerve gangliosides. This molecular mimicry mechanism can be attributed to some cases with atypical triggers such as Zika Virus or West Nile virus infections. Moreover there are accumulating clinical data for vector borne viral infections triggering GBS. We evaluated vector-borne viral infections in our GBS and AMAN patients. Eight patients with GBS, two patients with AMAN and as a control group, seven patients with normal pressure hydrocephalus were included. GBS and AMAN was diagnosed with clinical, electroneuromyograpic and cerebrospinal fluid (CSF) findings. Cerebrospinal fluid serum and urine samples were examined for vector borne viral infections via generic Flavivirus and Phlebovirus PCR. We also documented our patients prognostic scores such as Modified Erasmus GBS Outcome Score (mEGOS) and Modified Erasmus GBS Respiratory Insufficiency Score (mEGRIS).
The mean age of the patients was 56,8 (24-74 years) , six of them were female. All CSF, serum and urine samples of our patients and control patients were negative for Flavivirus and Phlebovirus families.
The preliminary results of our study in this our small cohort did not show any correlation between the vector-borne viral infections and GBS. Further studies with broad number of patients are needed for more suggestive results.

THE GENERATOR SITE IN ACQUIRED AUTOIMMUNE NEUROMYOTONIA

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Neuromyotonia (NMT) consists of spontaneous motor unit activity that reflects increased peripheral nerve excitability, leading to involuntary, persistent muscle activity, visible as muscle twitching at rest, with generalized, easily provoked cramps. Since the first electrophysiological (EMG) description of NMT by Denny-Brown and Foley (1948), there has been discussion about the origin of the abnormal electrical activity recorded in needle EMG studies. We studied two patients. Patient 1's NMT is aggravated by cold, and he has an associated non-progressive mild polyneuropathy with demyelinating features. He is now 73-year-old and has been followed in our centre for 20 years. He is negative for anti-VGKC antibodies. Firstly, he was treated with carbamazepine and phenylhydantoin with poor response, but he has shown major improvement on intravenous immunoglobulin (IVIg) during the last 15 years. Patient 2 is a 62 year-old man with NMT, followed for 1 year, with high titters of anti-VGKC antibodies (505 pmol/L; normal<72). He improved on IVIg during the last 12 months. Screening for neoplasia was unremarkable in both patients (negative anti-neuronal antibodies, in particular anti-Hu, anti-Yo and anti-Ri antibodies; normal computerized tomography scan of the chest and abdomen). In addition to routine studies, we tested synchronicity to spontaneous discharges in different motor units in simultaneous recordings made with two needle electrodes in the first dorsal interosseus muscle. Time-locked fasciculations in these double recordings would represent abnormal ectopic activity initiated in a nerve trunk with ephaptic stimulation of a nearby axon. In patient 1, this research protocol was applied once, 15 years after regular IVIg treatment. Patient 2 was investigated before and 1 year after IVIg. Both patients improved after IVIg, mirrored by a striking decrease in the amount of spontaneous activity on EMG. Moreover, our technique did not detect synchronous spontaneous activity (time-locked fasciculations) on the second assessment, although this was predominant before treatment in patient 2. In NMT, abnormal discharges originate both in distal axonal branches and in more proximal segments. It appears that IVIg is more effective in blocking antibody activity in proximal axonal segments, perhaps related to factors such as blood-nerve barrier, temperature or differing ion channel distributions.

PERIPHERAL NERVE INVOLVEMENT IN CELIAC DISEASE: A NOVEL ASSOCIATION WITH A MULTIFOCAL ACQUIRED MOTOR AXONOPATHY (MAMA)

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Celiac disease (CD) is a chronic, multisystem and immune-mediated disorder characterized by small-bowel sensitivity to dietary gluten in genetically predisposed individuals. Neurological manifestations may occur in about 10% of patients, including peripheral nerve involvement. Recent growing evidence strongly suggests that peripheral neuropathy in CD may be autoimmune and associated with anti-ganglioside antibodies. A 36-year-old woman presented with slowly progressive weakness of her right hand and fingers extensors. Medical and family history were unremarkable. On examination, muscle strength (Medical Research Council-MRC) was scored 0 for right wrist and finger extensors, 2 for right abductor pollicis longus and 4 for right ankle dorsiflexion. Right triceps brachii and brachioradialis reflexes were weak, but normal elsewhere. The remainder of the neurological examination was normal. Neuroaxis magnetic resonance was unremarkable, specifically with no gadolinium-enhancing lesions. Motor and sensory nerve conduction studies were normal. No conduction block or abnormal temporal dispersion was found. Needle electromyography showed severe neurogenic changes with abnormal spontaneous activity in right radial-innervated muscles, and chronic neurogenic changes in homolateral tibialis anterior, peroneus longus and extensor digitorum brevis. Ganglioside antibody testing was positive to IgG anti-GM2 antibody, but negative to anti-GM1 and other anti-ganglioside antibodies. Additional blood tests were unremarkable, in particular cryoglobulin testing was negative. Intravenous immunoglobulin improved weakness, as right extensors of the wrist and fingers scored 3 (MRC). A monthly treatment was initiated, which after 6 months was changed to every 2 weeks to preserve function. A diagnosis of MAMA was established. Later, CD was diagnosed in her daughter due to chronic diarrhoea. Our patient underwent anti-tissue transglutaminase antibodies determination and small-bowel biopsy after 7 years disease' duration, and a diagnosis of CD was made. Gluten-free diet was started, but her neurological picture did not change after six months. In our case the presence of IgG anti-GM2 antibody may support a causal link between MAMA and biopsy-confirmed CD, and the lack of response to gluten-free diet may be explained by chronic axonal injury induced by memory T-cells. This case broadens our knowledge about neurological manifestations in CD, raising a probable association with purely axonal multifocal motor neuropathies and anti-ganglioside antibodies.

FUNCTIONAL OUTCOMES OF SURGICAL INTERVETIONS IN ADOLESCENTS WITH CHARCOT-MARIE-TOOTH DISEASE: A DETAILED EVALUATION USING MOTION ANALYSIS

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Orthopaedic surgical intervention of the foot and ankle is performed in persons with Charcot-Marie-Tooth (CMT) for improving foot pain, ankle instability, orthosis fitting/comfort issues and shoe wear. The impact of these surgeries on ankle function during gait is not known. Therefore, the goal of this study was to measure gait changes in ankle function following surgical intervention by means of computerized motion analysis. Fourteen patients with CMT (10±4 years pre and 14±5 years post-operative) with bilateral orthopaedic surgery were included. All patients had a plantar fascia release plus some combination of other soft-tissue (posterior tibialis and tendo-Achilles lengthenings; extensor hallucis longus, peroneus longus and anterior tibialis transfers) and bony procedures (metatarsal and cuboid osteotomies). All patients completed two gait analyses (pre and on average 3.8 years post-surgery) during barefoot walking using a standardized 3D motion analysis protocol. The changes in ankle kinematics and kinetics and temporal-spatial parameters were analyzed in reference to a control group of patients with CMT without intervening surgeries with 2.2 years between gait analyses as well as normal reference data. The surgical group showed a significant increase in height between the pre and post-operative analyses and no changes in walking velocity (pre: 105±24, post: 103±21, normal: 127±10 cm/sec). Similarly, the ankle kinematics and kinetics showed no changes as a result of surgery. However, there was a trend for increased peak ankle dorsiflexion (pre: 13±9, post: 16±5, normal: 13±3 degrees). As in the surgical group, the control group showed an increase in height but no simultaneous increase in walking velocity (test 1: 102±18, test 2: 104±20 cm/sec). The control group also showed no changes in ankle kinematics and kinetics suggesting that the impact of the disease is, for the most part, not noticeable over 2.2 years. The results show that surgical intervention that primarily addresses foot alignment does not negatively impact ankle kinematics and kinetics during gait. The comparison with the control group supports this finding. However, there are some other findings such as the increase in peak dorsiflexion during stance in some patients that will need to be examined further in larger cohorts.

DO ORTHOSES IMPROVE GAIT IN CHILDREN AND ADOLESCENTS WITH CHARCOT-MARIE-TOOTH?

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Ankle-foot-orthoses (AFOs) are commonly prescribed for patients with Charcot-Marie-Tooth (CMT) to improve gait and reduce ankle instability and falling. There are no studies that examine bracing outcomes using objective evaluations. The purpose of this study was to examine the impact of various AFO designs on gait parameters in children and adolescents with CMT. We predicted that the AFOs would improve excessive and delayed peak dorsiflexion in stance and equinus in swing. Fifteen patients (mean age 12±5 years) were analyzed barefoot and with their prescribed AFOs by means of a standardized motion analysis protocol. A full clinical examination was also completed including strength and passive range of motion measures. The AFOs included solid, hinged and posterior leaf spring (tapered, less supportive) designs. Sagittal plane ankle kinematics and kinetics and temporal-spatial parameters were analyzed in comparison to normal controls. Walking velocity improved from 95±26 to 108±21 cm/sec demonstrating the functional benefits of AFOs. Ankle plantar flexion angle at initial contact improved from -8±8 to -1±4 degrees demonstrating improvement in drop foot in swing and at initial contact reducing the risk of tripping. However, the degree of peak ankle dorsiflexion in stance remained the same and excessive at 17±5 degrees barefoot and 16±5 degrees with AFOs suggesting that in many patients the AFO design was not sufficiently supportive. Peak ankle plantar flexor moment showed improvement from 0.69±0.29 to 0.79±0.25 Nm/kg highlighting the improved base of support provided by the AFOs that compensate for ankle plantar flexor weakness. However, peak power generation was reduced from 1.48±0.80 to 1.11±0.39 W/kg indicating that some of the available ankle strength was impeded with the AFOs. The results of this study suggest that orthoses can provide improved gait outcomes which will improve overall function. However, there are individual differences in patient impairment (strength, range of motion and bony deformity) and associated gait presentation that need to be accounted for in AFO design. AFOs do not always function as intended due to the complex interaction between patient impairment, orthosis stiffness and orthosis design. Motion analysis can assist in identifying the specific AFO needs for an individual with CMT.

HEAD AND VOICE TREMOR IMPROVING WITH IMMUNOTHERAPY IN AN ANTI-NF155 POSITIVE CIDP PATIENT

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune neuropathy with a heterogeneous clinical spectrum. Specific autoantibodies define different clinical phenotypes. CIDP with NF155 antibodies constitutes a specific CIDP subset in which a high incidence of postural and intention tremor has been described and that responds poorly to immunoglobulins. We report a patient with an anti-NF155 positive CIDP that presented head, voice and limb tremor that improved with immunotherapy.

A 64-year-old man with unremarkable medical history, presented at the age of 61 with progressive distal weakness and paraesthesia. Numbness, gait ataxia and action tremor involving voice, head and limbs appeared sequentially. The EMG showed features of acquired demyelination fulfilling CIDP diagnostic criteria. A first course of intravenous immunoglobulins was ineffective. The weakness, ataxia and tremor worsened significantly, needing two walking aids first and becoming wheelchair bound later on. He received six plasmapheresis cycles that were also ineffective and oral corticosteroids (1mg/Kg) were started with mild improvement. After corticosteroid tapering the patient developed a severe relapse and was referred to our centre. Five plasma exchange cycles followed by rituximab (375mg/m2, 6 doses) were added to the corticosteroids. Three months later the weakness, ataxia and tremor, including the head and voice tremor, started to improve significantly. Six months later the patient presented a significant improvement and was able to walk unaided. The anti-NF155 antibody titres fell from 1/72900 pre-rituximab to be undetectable.

Limb tremor is known to occur in patients with inflammatory neuropathies and, specifically in anti-NF155+ CIDP patients but, to our knowledge, this is the first report of a CIDP patient presenting with head and voice tremor ever reported. The improvement of tremor with immunotherapy strongly suggest that anti-NF155 autoantibodies are involved in its pathogenesis, expanding the phenotype of anti-NF155 specific clinical features.

CHARCOT–MARIE–TOOTH DISEASE TYPE 2G REDEFINED BY A NOVEL MUTATION IN LRSAM1

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Charcot-Marie-Tooth disease type 2G is an autosomal dominant and slowly progressing inherited neuropathy which was first described over 30 years ago. It has been attributed to a single Spanish family consisting of 33 individuals with 13 affected members spanning four generation. Initially, the genetic defect was linked to a 13.2Mb region in 12q12-q13.3. However, extensive sequence and structural variant analyses using whole genome sequences (WGS) of

three affected individuals did not reveal any known or novel genetic causes within the region. Over the last decade, serial clinical re-evaluation of the entire pedigree was performed leading to changes to the affection status of seven individuals redefining the disease-linked region to chr9q31.3-q34.2 (Z_{max} = 4.39 at *Theta* = 0). Additional family members were then submitted for whole exome sequencing. This has led to the identification of a novel missense variant in the E3 ubiquitin-protein ligase LRSAM1 (p.Cys694Tyr) that was previously not covered by WGS. The variants co-segregated with disease and were absent from controls. Other mutations that are known to disrupt the RING domain of LRSAM1 have been previously reported to cause both autosomal dominant and recessive CMT type 2P (CMT2P). Unlike prior reports, we demonstrated that the mutation does not influence overall protein levels of LRSAM1, nor of its ubiquitylation target TSG101 in patient derived lymphoblasts. Transcriptomics analysis identified significant upregulation of another E3 ubiquitin-protein ligase (NEDD4L) and of a key regulator of axonal degeneration (TNFRSF21). Notably, magnetic resonance imaging of lower-limb musculature systematically showed fatty atrophy in both clinical and subclinical mutation carriers emphasizing its use for the identification of mildly affected members. Our findings demonstrate that the isolated genetic entity CMT2G is caused by a missense mutation in LRSAM1 and should be reclassified as CMT2P. Moreover, we reveal novel molecular players associated with LRSAM1 dysfunction, and highlight pathways and therapeutic targets shared with amyotrophic lateral sclerosis and Alzheimer disease.

TRPV1 EXPRESSION IN HUMAN PERIPHERAL SENSORY NERVES AND RELATIONSHIP TO NEUROPEPTIDES CGRP AND SP

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Damage to peripheral nerves is a prerequisite for neuropathic pain. However, it remains unclear why some neuropathy patients have pain, but others with identical nerve conduction, QST and IENFD do not. We propose to examine the distribution of TRPV1 and its co-localization with CGRP and SP in epidermal nerve fibers in patients with and without neuropathic pain. We aimed to define the expression pattern of TRPV1 in normal healthy subjects first, and study the co-localization of TRPV1 with CGRP and SP in normal controls and patients with painful neuropathy. Skin biopsies from neuropathy patients and normal subjects were utilized. Anti-TRPV1 antibody generated in our university with support from NINDS-funded Dept. of Neuroscience Monoclonal Core (NS050274) was used. Combined immunohistochemistry were performed to identify co-expression of TRPV1 with CGRP, SP and PGP 9.5. The distribution of TRPV1 in controls revealed a proximal to distal gradient similar to that observed for IENF labeled by PGP 9.5. TRPV1 staining was more intense in nerve terminals in the epidermis. Combined immunostaining revealed that 65% of PGP 9.5 labeled fibers in the epidermis were TRPV1+, while 78% of CGRP+ fibers TRPV1+. Patients with pain had a higher density of TRPV1+ fibers compared to that of patients with numbness. A greater proportion of CGRP+ fibers (94%) in the painful patients were TRPV1+. Expression of TRPV1 in controls exhibits a distal to proximal gradient. TRPV1 expression and co-localization with CGRP were altered in neuropathic pain patients, suggesting that this receptor plays an important role in pathological states.

NOCICEPTIN/ORPHANIN FQ OPIOID PEPTIDE (NOP) RECEPTOR EXPRESSION IN PACHYONYCHIA CONGENITA (PC)

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Activation of the NOP-receptor (NOP-R) by its endogenous ligand nociceptin/orphanin FQ or non-peptide agonists modulates nociception and analgesia in neuropathic pain models. The wide distribution of NOP-R and its endogenous ligand represents an attractive treatment target. Since pain is the most prominent feature in PC, we defined expression of the NOP-R in plantar skin biopsies and assessed whether alterations exist in PC–affected vs PC-unaffected and anatomically matched control skin. Skin biopsies from k6a PC and control subjects were immunohistochemically stained for NOP-R. Combined immunostaining for NOP-R with PGP 9.5, neurofilament H (NFH) and CGRP was used to define NOP receptor expression in the epidermis and upper dermis. Robust NOP-R was detected in epidermal keratinocytes and a subset of PGP9.5+ fibers in both epidermis and dermis. Staining was inhibited through pre-incubation with a NOP-R blocking peptide and western blot analysis using homogenized human skin tissue demonstrated a band at ~50kd consistent with NOP-R molecular weight. NOP-R expression occurred in dermal NFH+ A beta-fibers in all groups though no CGRP+ fibers co-expressed NOP-R. PC-affected skin had slightly lower NOP-R expression than in PC-unaffected skin and a similar pattern in anatomically matched locations from healthy control subjects was observed. NOP-R is expressed in human plantar skin epidermal keratinocytes as well as a subset of epidermal and dermal nerve fibers. These fibers are PGP 9.5+, CGRP- and many co-express NFH. NOP receptor is a viable pharmaceutical analgesic target in PC patients irrespective of its slight down-regulation as compared to PC-unaffected skin. *This work was supported by Grünenthal GmbH.*

A MULTICENTRE RETROSPECTIVE STUDY OF CHARCOT-MARIE-TOOTH DISEASE TYPE 4B (CMT4B)

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CMT4B1 and B2 are characterized by recessive inheritance, early onset, severe course, slowed nerve conduction, myelin outfoldings, association with loss-of-function mutations in Myotubularin-related protein-2 and -13 (MTMR2, MTMR13/SBF2), respectively, involved in the metabolism of PtdIns3*P* and PtsIns(3,5)P_2 phosphoinositides, key regulators of membrane trafficking. In a multicentre retrospective study to better characterise CMT4B, we collected a minimal dataset of information including CMTES/CMTNS on 41 CMT4B patients, 27 CMT4B1 (14 unrelated families) and 14 CMT4B2 (11 families). CMT4B1 patients were younger and with earlier onset than CMT4B2: last visit was performed at a mean age of 22 years (SD 12.5; range 1-48) for CMT4B1 and 35 years (13.1; 16-59) for CMT4B2; disease onset occurred at a mean age of 2.8 years (3.2; 0-13) in CMT4B1 as compared to 5.9 years (5.3; 1-20) in CMT4B2; delay in motor milestones occurred in 15/26 CMT4B1 and 4/14 CMT4B2 subjects. Eleven CMT4B1 patients became chair-bound, whereas all CMT4B2 subjects but one are still ambulant, although with AFOs for 9 patients and requiring unilateral support in two cases. Both disease types are characterised by vocal cord involvement (9/26 CMT4B1 and 6/14 CMT4B2); respiratory involvement was seen almost exclusively in CMT4B1 patients (n=8, four requiring non-invasive ventilation and one tracheostomy, as compared to one CMT4B2 patient on NIV at age 49); two CMT4B1 subjects and an affected CMT4B1 relative not included in the present study died of respiratory complications. Glaucoma (n=4) and buphthalmos (n=2) occurred only in CMT4B2. CMTES/ CMTNS scores were higher in CMT4B1 patients in spite of their younger age, indicating more severe disease: CMT4B1 = CMTES mean 17.9 (n=20; SD 6.0; range 8-28/28), CMTNS mean 30.2 (n=10; SD 4.8; range 19-36/36,; CMT4B2 = CMTES mean 16 (n=13; SD 5.0; range 6-26/28), CMTNS mean 25 (n=12; SD 4.7; range 19-34/36). Our data confirm that CMT4B1 is more severe than CMT4B2. Interestingly, MTMR2 interacts with MTMR13. MTMR2 is a catalytically active phosphatase, whereas MTMR13 is a catalytically inactive protein, known to increase MTMR2 enzymatic activity. Thus, in CMT4B2 nerves a residual enzymatic activity of MTMR2 may result in a less severe clinical phenotype as compared to CMT4B1.

PREGNANCY, SLEEP, FATIGUE AND OTHER ITEMS IN CHARCOT-MARIE-TOOTH DISEASE: DATA FROM QUESTIONNAIRES LINKED TO THE ITALIAN CMT NATIONAL REGISTRY

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The Charcot-Marie-Tooth disease (CMT) National Registry is fully operative (https:www.registronmd.it) with collection of clinical/genetic information (minimal dataset) and reporting of clinical scales; 537 CMT patients have registered thus far and have chosen one of the 9 reference centers; information collected during the *ad hoc* visit have been entered in the Registry for 420 of them. Registered patients have the chance to participate to a study that requires filling online self-reported questionnaires related to five important issues: disease course and complications during pregnancy; use, efficacy and tolerability of orthotics and assistive devices; outcome of surgery for skeletal deformities; safety of anesthesia; occurrence of sleep disorders (including evaluation of fatigue, anxiety and depression). By February 2016, 201 patients and 36 relatives/friends (as healthy controls) have filled the questionnaires. We are performing a first explorative analysis of results, but data collection on all questionnaires will be prolonged until Novemebr 30, 2017, to obtain a larger sample. Pregnancy: 46/73 CMT women had at least one pregnancy; complications ranging from mild to severe occurred in 44/108 pregnancies vs 9/42 in controls. CMT worsened in 7 pregnancies (6 patients) with no recovery in 5 instances. Prenatal diagnosis was performed in 8/108 pregnancies. Satisfaction related to surgical procedures for foot

deformities, assessed with VAS (score 0-10), was 6.4±3.5 (n = 110). Repeat surgery was required in 9/72 instances. Sleep: the Epworth Sleepiness Scale questionnaire revealed abnormalities of sleep in 44/142 CMT patients (31%) and in 5/30 controls (17%). The vast majority of CMT subjects (123/138; mean 9.1 ± 3.2), but also of controls (27/30; 8.6 ±2.9) were not good sleepers according to the Pittsburgh Sleep Quality Index (PSQI) (range 0-21, 0 good sleep). Fatigue: scores of Modified-Fatigue Impact Scale (range 0-82, 0 no fatigue) were higher for CMT (mean 33±18.2) than controls (mean 16.6±12.5). Hospital Scale for Anxiety and Depression: 63/138 CMT subjects had mild-to-severe anxiety and 35/138 mild-to-severe depression as compared to 7/29 and 4/29 controls, respectively. Data analysis on orthotics and anesthesia is ongoing. In conclusion, the first data analyses confirm that there are problems related to all the five domains explored, that will need to be specifically addressed in patients' care. Supported by Telethon-UILDM grant GUP13006.

CLINICAL SIGNIFICANCE OF CONDUCTION BLOCK IN CMT1A PATIENTS WITH PMP22 DUPLICATION

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Charcot-Marie-Tooth disease (CMT) is the most frequent motor and sensory peripheral neuropathy and is known to have the uniform demyelination. The traditional definition of conduction block is the reduction of negative peak of compound muscle action potential (CMAP) of proximal segment relative to adjacent distal segment more than 50%. In this study, we tried to find the frequency of conduction block in CMT1A patients and to investigate the differences of the clinical manifestation. We enrolled unrelated 48 CMT1A patients (26 males and 22 females) with PMP22 duplication and undertook nerve conduction studies from 2011 to 2015. Stimulation sites were wrist, elbow and axilla for median nerve study. Eleven patients (22.9% of all enrolled patients) had NCS features suggestive of conduction block. Compared to CMT1A patients without conduction block, functional disability scale was significantly higher in CMT1A patients with conduction block ($p < 0.05$). However, onset age and disease duration were not different between CMT1A patients with and without conduction block. In addition, conduction block was more frequently observed in distal segments than proximal segments. We suggest that the frequency of conduction block in CMT1A patients is not low, and there is some heterogeneity of demyelination in CMT1A patients. Also, in CMT1A patients, the conduction block might have relationship with clinical disability.

SUBACUTE COMBINED DEGENERATION CAUSED BY CHRONIC ATROPHIC GASTRITIS WITH SPURIOUS ELEVATION OF VITAMIN B12 LEVEL

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The subacute combined degeneration (SCD) is diagnosed by a characteristic clinical manifestation, spinal MRI, and decreased serum vitamin B12 levels. We report a case of SCD with elevated homocysteine and methlymalonic acid level in the situation of spurious elevation of vitamin B12 concentration. An 80 years old man presented with progressive gait disturbances and sensory disturbances. About a year ago, he felt both hands and feet paresthesia and gait disturbances. Four months before the visit, nerve conduction tests were performed elsewhere due to symptoms. Polyneuropathy was found. The laboratory test showed megaloblastic anemia. However, serum vitamin B12 concentration was increased to 1649 pg / mL (normal: 200-950 pg / mL). His symptoms progressed gradually. At presented, neurological examination showed spasticity of the lower limb without weakness, and vibration and position sensation were decreased in both lower limbs, and showed ataxic gait. Spinal cord MRI showed a lesion with a long T2 high signal intensity from C1 to T4 in the posterior column of the spinal cord. Further laboratory test were added, then while folate was normal level but homocysteine at 21.2 umol/L (normal: 5-12 umol/L), and methylmalonic acid at 2.9 uM / L (normal: 0-0.4 uM / L) were increased. Finally, SCD caused by vitamin B12 deficiency was diagnosed. In addition, gastric endoscopy was performed to find the cause of vitamin B12 deficiency and chronic atrophic gastritis was found. After cobalamine treatment for 6 months, hemoglobin level was improved and his symptoms were all improving with a little gait disturbances. False-elevation of vitamin B12 level could lead to delayed diagnosis and cause irreversible changes in the nervous systems. One of the most commonly used methods to measure vitamin B12 concentrations is competitive-binding assay, which may result in normal levels even with vitamin B12 deficiency due to the effect of anti-intrinsic factor antibodies. When vitamin B12 deficiency is suspected, even if the vitamin B12 concentration is normal, additional tests of homocysteine and methylmalonic acid should be considered.

CLINICAL AND GENETIC HETEROGENEITY IN CHARCOT-MARIE-TOOTH NEUROPATHY TYPE 2 PATIENTS FROM TURKEY

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Hereditary motor and sensory neuropathies, also called CMT neuropathies, are the most common

group among the hereditary neuropathies. CMT subtypes are grouped by axonal, demyelinating or intermediate phenotype, or by autosomal-dominant (AD), autosomal-recessive (AR) or X-chromosomal inheritance. CMT-2 is considered axonal and characterized by distal muscle wasting, mild sensory loss and normal or near-normal nerve conduction velocities. Mutations in more than 18 genes are known to be able to cause autosomal dominant (AD) or recessive (AR) CMT-2 to date. The genetic heterogeneity in Charcot-Marie-Tooth (CMT) is a challenge for genetic diagnostics. Clinical clues and frequencies of mutations in CMT genes from large cohorts may help to develop strategies for efficient genetic testing. Here, we present the clinical, electrophysiological and genetic features of 31 patients from Turkey, diagnosed as genetically confirmed CMT-2 in the Department of Neurology, Istanbul Faculty of Medicine our clinic between 1990 and 2015. Genetic testing was performed for GDAP1 by DNA sequencing and samples from 16 patients were exome sequenced (WES). Twenty-one male and ten female patients from 16 unrelated families were investigated. Segregation was AR in eight, AD in six families and two were isolated cases. Intra- and interfamilial variability in the age of onset with a range of 2-48 (mean 12.6 ± 9.8 years) and disease progression rate were striking. Slowly progressive weakness and atrophy of distal muscles in the feet and/or hands were the most common presenting symptoms. *MFN2* was found in four unrelated AD kinship and in 2 unrelated AR kinships and was most common gene mutated among whole cohort. *GDAP1* was the most commonly mutated gene among AR families (5/8). WES revealed further mutations in *AARS*, *NEFL*, *KIF1B* and *HSPB1*, however, the causative mutation could not be identified in known CMT2 genes in about 40% of patients. Our data indicates the marked intra- and inter-familiar phenotype variability in CMT-2 as previously described in literature. Many more genes causing ARCMT-2 remain to be discovered.

PAIN AND ANXIETY WITH ELECTRODIAGNOSTIC PROCEDURES

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Electrodiagnostic (EDX) studies involving electromyography/nerve conduction study (EMG/NCS) are useful for diagnosis of neuromuscular disorders. Although these are safe procedures, EMG and NCS often evoke anticipated pain and anxiety. There are no published research studies to support the notion that providing detailed information to patients prior to these procedures would reduce procedural pain and ameliorate anxiety levels afterwards. The objective of this study was to perform a prospective survey to assess anticipated pain and anxiety in patients presenting for EDX studies, design a detailed patient education form, and assess the change in perceived pain and anxiety pre and post procedure in the standard of care (SOC) education versus the printed detailed education instrument group. After completing a brief pain/anxiety questionnaire, patients were randomly assigned to either SOC verbal education group or to read the detailed education form. Another brief questionnaire was completed post procedure. Seventy-eight patients were enrolled at the time of abstract submission, 41 in intervention and 37 in SOC groups. Mean age of patients enrolled was 58±15 years. Pain was anticipated by 81% patients as a visual analog scale (VAS) score mean of 4.9±2.5 with no significant difference between both groups (p=0.86). Post-procedural pain was reported in 75% of patients with mean pain score of 5.3±2.2 and no significant difference between the two groups (p=0.09). Anxiety pre-procedure was reported by 35% patients with a mean Likert-like score of 5.3±2.2 score in all cases (p=0.12 between both groups). Post-procedural anxiety frequency was reduced to 8% with mean level of 4.5±2.6 (p=0.72 between both groups). Most patients reported pain with both EMG and NCS (53%). We found that EDX testing evokes moderate pain in most and in some cases moderate anxiety level. The detailed education intervention did not attenuate the frequency or severity of pain. Post-procedural anxiety was expectedly reduced in severity and frequency in both groups with a suggestion that anxiety severity is lesser in the detailed education group but numbers were small. Further studies with more detailed questionnaire and perhaps web-based education in larger population may be useful to reduce pain/anxiety in patients presenting for EDX studies.

CIDP DIAGNOSTIC CRITERIA AND TREATMENT RESPONSE

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Diagnostic criteria for chronic inflammatory demyelinating polyneuropathy (CIDP) have been designed for use in clinical trials. There is limited data on the comparative diagnostic utility of these criteria in the clinic setting and it is unknown if some of these criteria are better for predicting treatment response. The objective of this study is to compare the sensitivity of various diagnostic criteria and review treatment response. After obtaining local IRB approval, we performed a retrospective chart review of CIDP patients seen at the University of Kansas Medical Center between 2008 and 2014. We abstracted the clinical, electrodiagnostic, and treatment information. We determined the frequency of patients fulfilling each of the following criteria: EFNS 2010, AAN, Saperstein and INCAT. We defined treatment response based on treating physician's impression of change, patient–reported functional improvement or one point grade change in the MRC grade. Fifty-three CIDP patients charts were reviewed, 15 were excluded due to missing data. Mean age was 51.5, and 16(42%) were female. Elevated CSF protein was seen in 18/23(78%).

Twenty-eight (73%) fulfilled EFNS definite criteria, 5 (13.16%) EFNS probable, 10 (26.3%) AAN, 20 (52.6%) INCAT, and 20 (52.6%) the Saperstein criteria. Treatment response in patients who fulfilled EFNS definite/probable criteria included 20/22 to IVIG, 5/8 to IV or oral corticosteroids, 2/3 to mycophenolate mofetil; among patients who fulfilled AAN criteria, these were respectively 8/9, 2/3 and 1/1; among those meeting INCAT criteria 10/15, 5/7 and 1/2; and for Saperstein criteria it was12/17, 4/6 and 1/2. Half to two-thirds of patients responded to PLEX based on different criteria. While all CIDP criteria can similarly predict IVIG treatment response, the EFNS 2010 criteria are most sensitive for the clinical diagnosis of CIDP.

ROLE OF THE ALPHA SECRETASE TACE DURING WALLERIAN DEGENERATION

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Axonal NRG1 type III is an essential instructive signal for PNS myelination, since its expression determines whether axons are myelinated and also the thickness of the myelin sheath. Previous studies have shown that secretases' cleavage controls NRG1 type III activity at post-transcriptional level. Specifically, the beta-secretase BACE-1 cleavage of NRG1 type III promotes myelination, whereas the alpha-secretase TACE inhibits PNS myelination by inactivating NRG1 type III.
After a damage, the axon located distally to the site of injury degenerates and loses the myelin sheath, following a process termed as Wallerian degeneration. Unlike the CNS, axons in the PNS can regenerate and regrow. Several studies have shown that regeneration is favored by the trans-differentiation of Schwann cells, which start to create a permissive environment for axonal regrowth. In addition, it has been shown that NRG1 regulates the early stages of the dedifferentiation process and is essential for creating a permissive environment to regeneration. Similarly, the beta secretase Bace-1 promotes PNS regeneration and remyelination.
In the present study, we analyzed the role of the alpha-secretase TACE during Wallerian degeneration. Our data indicate that TACE is upregulated in sciatic nerves after injury, distally to the site of damage. Since TACE is expressed in Schwann cells and axons, we analyzed the role of both glial and neuronal TACE during degeneration and regeneration processes. Thus, we performed crush injury in sciatic nerves of two different transgenic lines carrying a conditional deletion of TACE either in Schwann cells (P0-Cre//TACE$^{flox/flox}$) or in neurons (Chat-Cre//TACE$^{flox/flox}$). The analyses of the different phases of the Wallerian degeneration in these animals suggest a role of glial TACE during the early stage of the process. In fact, we observed an increased number of myelinated axons only in P0-Cre//TACE$^{flox/flox}$ mice, while we did not detect substantial differences in mutant ChatCre//TACE$^{flox/flox}$ mice. These results suggest that even during regeneration TACE has an inhibitory role, as deletion of TACE in Schwann cell likely induces the activation of a neuro-protective program that we are currently investigating.

ARL6IP1 CAUSES CONGENITAL INSENSITIVITY TO PAIN, SELF-MUTILATION AND SPASTIC PARAPLEGIA

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The hereditary sensory and autonomic neuropathies (HSAN) constitute a clinically and genetically heterogeneous group. HSAN are associated with sensory dysfunction, altered pain and temperature perception with varying degrees of autonomic dysfunction, and abnormal small fibers neurodevelopment. More than ten genes have been described so far in the HSAN group. Original classification encompassed four entities, but additional subgroups continue to be described. Hereditary sensory neuropathies (HSAN) type II are characterized by autosomal recessive inheritance, onset at birth and self-mutilating behavior. Until now, one homozygous frameshift variant, c.[577_580del], p.(Lys193Phefs*37), was reported in *ARL6IP1* (ADPrRibosylation-like factor 6-interacting protein 1) in a consanguineous family. Patients presented with spastic paraplegia, diffuse sensory and motor polyneuropathy and acromutilation. The disorder was classified as autosomal recessive spastic paraplegia SPG61. Here, we described a new patient with congenital insensitivity to pain, sensory neuropathy, self-mutilation, and spastic paraplegia. Whole exome sequencing showed a homozygous frameshift variant c.[577_580del], p.(Lys193Phefs*37) in *ARL6IP1*. The protein harbours reticulon-like short hairpin transmembrane domains and has a role in endoplasmic reticulum shaping. The variant causes an additional C-terminus hydrophobic domain which could alter its function. Arl6ip1 interacts with atlastin-1 responsible for SPG3A and HSAN type 1D. This report highlights the role of *ARL6IP1* in pathophysiology of insensitivity to pain and spastic paraplegia.

SEQUENTIAL EDX TESTING IDENTIFIES DIFFERENTIAL SUSCEPTIBILITY OF THE MEDIAN NERVE TO PROLONGED WRIST EXTENSION IN NORMAL SUBJECTS

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Carpal tunnel syndrome (CTS) is responsible for sensory and/or motor symptoms that may be increased by wrist flexion or extension (Phalen sign). Previous studies have shown that short duration (*e.g.*5 min or less) flexion or extension was not responsible for significant changes of median nerve conduction parameters. The objective is the study was to determine how prolonged extension (reverse Phalen's test) affects median and ulnar nerve conduction parameters in normal subjects. After providing informed consent, 30 normal subjects (17 females, age rank 18-55 years) underwent motor and sensory testing of both median and ulnar nerves from the dominant side. EDX testing was performed using standard techniques with wrist in neutral position, then during passive wrist extension (90°) for 30 minutes, with sequential recording of both motor action potential (CMAP) and sensory action potential (SNAP) latencies and amplitudes every 5 minutes after extension onset. Ulnar nerve conduction parameters remained unchanged in all the subjects. Regarding median nerve, 4 groups of subjects could be individualized: 12 subjects with no changes; 8 subjects with only significant decrease of SNAP amplitude (-50%); 6 subjects with both SNAP amplitude and velocity decrease; 4 subjects with both CMAP and SNAP significant changes. When present, changes did not appear before 10 min, with SNAP decrease being the earliest observed abnormality. Prolonged wrist extension was responsible for median nerve EDX parameter modifications in 18/30 normal subjects. Sensory fibers were firstly affected, corresponding to the chronology clinically encountered in CTS. Based upon these results, the same protocol will be used in patients presenting with mild clinical CTS, in order to try and identify an additional EDX technique being useful in the diagnosis of CTS. One could also wonder whether the subjects with the most important changes would be more prone to present CTS in the future.

DETERMINING THE PATHOGENICITY OF NEWLY IDENTIFIED *ATP7A* VARIANTS USING PRIMARY FIBROBLASTS

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Mutations in the *ATP7A* gene cause of X-linked hereditary distal motor neuropathy (dHMNX). To date, missense mutations (T994I and P1386S) in this copper transporting ATPase are the only confirmed mutations causing dHMNX in two independent families. Next generation sequencing (NGS), including whole exome and whole genome sequencing, is increasing the rapid detection of variants in genes known to cause disease, however the absence and size of additional families, make it challenging to determine the pathogenic or benign status of variants identified. We have recently identified new variants in *ATP7A* in patients with progressive peripheral neuropathy, suggesting further genetic heterogeneity of dHMNX. Two of these new variants, pE840V and pM1311V, are located at highly conserved amino acids within domains of ATP7A (A-Domain and P-Domain, respectively) that are critical for the catalytic cycle of the copper transporter. We have also identified a third variant (c.3802-9A>G) located 9 bases upstream exon 19 that is predicted to abolish a conserved branch-site, a consensus intronic sequence necessary for the processing of immature RNA during splicing.

Our recent investigations using both patient fibroblasts and an Atp7a conditional knock in mouse model for dHMNX expressing Atp7a^{T985I}, the orthologue of the human ATP7A T994I mutation, showed reduced ATP7A protein levels and defective retrograde trafficking of ATP7A, as pathological hallmarks of dHMNX ATP7A causative mutations. To elucidate if the newly identified pE840V, pM1311V and c.3802-9A>G *ATP7A* variants are pathogenic, we have systematically assessed patient fibroblasts harbouring these mutations for altered parameters previously found in the pathogenic T994I ATP7A mutation.

We predict that functional characterisation of ATP7A using patient fibroblasts harbouring newly identified variants will provide the evidence to ascertain whether these variants are disease causing. Establishing a systematic functional readout for *ATP7A* variants will improve accuracy of genetic counselling and patient management of dHMNX in those cases where genetic evidence is limited. This study represents a complementary and necessary approach to the use of NGS, for validating the pathogenic status of variants identified and for expanding the genetic heterogeneity of dHMNX.

MONTH OF BIRTH AS A RISK FACTOR FOR GUILLAIN-BARRÉ SYNDROME

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Month of birth (MOB) have been defined as a risk factor for more than 50 diseases. For instance, susceptibility for multiple sclerosis (MS) seems to be associated with being born in May, while lower risk of MS is observed in those born in November. There are no studies that assessed potential association between MoB and a risk for Guillain-Barré syndrome

(GBS). We sought to determine if the risk of GBS is associated with the MoB. Study included 446 GBS patients diagnosed in Serbia, Montenegro and Republic of Srpska in the period from January 1, 2009 until December 31, 2015. MOB of patients and of general population were compared. Patients with GBS had tendency to be born in October (27% increase compared to general population, p=0.07) and were less likely to be born in June (28% decrease, p=0.05). When consider specific seasons, GBS patients were more likely to be born in winter months (16% increase, p<0.05). No associations were found between month/season of birth and disease severity. Results of this pilot study showed that GBS patients are more likely to be born in cold months, and less likely to be born in June. This might be explained by higher exposure to different pathogens during pregnancy in cold months. In accordance with this, it is well known that early exposure to infective agents reduces risk of allergic and autoimmune diseases. Further studies are needed to test our findings in different cohorts and in regions with different climate. These results may shed new light on the disease pathogenesis.
Key words: Guillain-Barré syndrome, month of birth, season, risk, severity

GUILLAIN-BARRÉ SYNDROME – ACUTE DISEASE WITH CHRONIC CONSEQUENCES

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Majority of patients with Guillain-Barré syndrome (GBS) tend to have a successful recovery, but in number of them significant long-term consequences may negatively affect their quality of life. Aim of this research was to analyze the outcome of the disease one year after the acute episode of GBS. Among 82 patients diagnosed with GBS in seven tertiary centers in Serbia, Montenegro and Republic of Srpska during 2014, 57 subjects were retested after one year (62% males, mean age 57±16 years). Functional disability of patients was estimated based on the GBS Disability Scale (GDS). Severe form of the disease (GDS score 4-6) was registered in 50% of patients at admission, 73% at nadir, and 24% on discharge. After one year follow-up period, 14% of patients had no symptoms of GBS, 42% had mild symptoms, 24% was able to walk but not to run, 8% needed unilateral support during walking, while 3% was wheelchair bound or bedridden. Lethal outcome was registered in three patients during acute phase of GBS and in four more during one-year follow-up. Paresthesias were present in 60% of GBS patients, musculoskeletal pain in 40%, and fatigue in 21% one year after acute phase of the disease. Factors associated with the worse functional outcome (GDS grade above 1) after one year were: age above 70, preceding respiratory infection, and worse GDS on discharge. One year after the onset of the disease, significant number of our GBS patients had neurological impairments including sensory symptoms, pain, fatigue and muscle weakness which may significantly affect patients' everyday functioning.

HOMOZYGOUS DUPLICATION OF *PMP22*: A CASE REPORT

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Charcot-Marie-Tooth (CMT) disease, also known as hereditary motor and sensory neuropathy, is a heritable peripheral neuropathy caused by genetic mutations in many different genes. CMT type 1A is the most common form of CMT. Individuals affected with CMT1A commonly have distal muscle atrophy, foot deformities, abnormal gait, and reduced nerve conduction velocities caused by demyelination of the peripheral nerves. CMT1A is known to be caused by a duplication of the *PMP22* gene at 17p11.2. The proposed disease mechanism of CMT1A is believed to be increased gene dosage of the *PMP22* gene, although the exact function of *PMP22* is not known. There have been previous reports in the literature of individuals who carry a homozygous duplication of *PMP22*, therefore having four copies of the gene. However, many of these reports have focused on adult patients who symptoms may not vary significantly from individuals who harbor only a duplication of *PMP22*. A 23 month old male presented to the University of Iowa Hospital due to a family history of CMT1A and concern for delay in independent ambulation. He was known to have both a maternal and paternal family history of CMT1A, although the families were believed to be unrelated. On exam he was unable to walk independently, but could take a few steps when his hands were held. Per report he began crawling and scooting at 18 months of age. He was not found to have any structural abnormalities or atrophy in his upper or lower extremities. Electrodiagnostic testing revealed a demyelinating neuropathy. Only one nerve was tested, as the patient was unable to tolerate additional shocks. The peroneal nerve was found to have a nerve conduction velocity of 7 m/s. Based on the clinical presentation, electrodiagnostic examination and family history deletion and duplication testing for *PMP22* was performed. This testing revealed a homozygous duplication of *PMP22*, which has been previously reported to cause CMT1A. This case supports the gene dosage disease mechanism, as our patient appears to be more severely affected than a typical infant or toddler affected with CMT1A.

CMT1B AND SENSORY ABNORMALITIES ASSOCIATED WITH A MPZ NULL MUTATION

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MPZ mutations are associated with the demyelinating early-onset Charcot-Marie-Tooth (CMT) type 1B and with the axonal later onset CMT2I/CMT2J. Paresthesias/dysesthesias and pain have been already reported in some CMT types and also in CMT2I/J. We report 16 patients (13 from 5 families, 3 sporadic cases,) carrying the *MPZ* c.306delA mutation (p.Asp104ThrfsTer14). This is predicted to be a loss-of-function mutation, leading to P0 haploinsufficiency. Most of the subjects have genetic *ancestry* from Puglia region (Southern Italy). Two patients carried the mutation in homozygosity, showing a severe phenotype: onset at birth, severe scoliosis, proximal weakness, distal limb plegia, no autonomous walking, CMT Examination Score (CMTES) 23-25/28. All the other heterozygous patients had mild adult-onset (mean age 33, range 20-56) neuropathy, walked without aids or ankle-foot orthoses, had CMTES <4/28. Five showed mild foot deformities, 5/16 had foot and 7/16 hand weakness (MRC never less than 3/5), 10/16 sensory loss in lower limbs (LL). Paresthesias/dysesthesias (mostly tingling and burning in type) localized in hands and LL were reported by 15/16 subjects, neuropathic pain by 10/16. In the homozygous patients, all CMAPs and SAPs were absent. In all other subjects, motor conduction velocities (CV) were >31 m/s (range 31-50 m/s) and sensory CV >29 m/s (range 29-62 m/s). CMAPs as well as SAPs were normal or moderately reduced in amplitude, indicating only slight axonal loss. We confirm that heterozygosity is associated with very mild CMT, whereas homozygosity causes a very severe neuropathy. Our data suggest that paresthesias and neuropathic pain are very common and should be considered as part of the phenotype. Although the clinical picture suggests a small fiber neuropathy, no such evidence is provided in the current literature. In the attempt to further investigate this field, we found in a 37-year-old male patient of our series that all thresholds were increased at quantitative sensory testing, and several abnormalities of small nerve fibers were present in skin biopsy. Apparently, P0 aneuplody causes neuropathy and small fiber involvement through a mechanism different from other *MPZ* missense mutations.

A NOVEL PROTEIN, MAJOR URINARY PROTEIN (MUP) CONTRIBUTES TO THE BEHAVIOUR OF DIABETIC AND NONDIABETIC SENSORY NEURONS

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A microarray mRNA analysis of dorsal root ganglia examined in long-term diabetic mice yielded an unexpected upregulation of a unique set of proteins known as Major Urinary Proteins (MUPs 1&2). Originally, this family of barrel shaped proteins was described as including mediators of pheromone secretion in the urine of rodents, apparently unconnected to other functions. We identified its unanticipated expression in sensory neurons of adult mice and rats and explored its potential impact on the properties of these neurons. Analysis of rat and mouse sensory neurons showed widespread and pan-neuronal cytosolic MUP expression, not only in the cell body, but also in distal sensory projections located in the dermis of the footpad. To assess the role that MUP might offer in the growth behaviour of adult neurons, we examined siRNA-induced knockdown of MUP on pre-injured dissociated DRG primary cultures. MUP knockdown in both species showed a significant increase in neurite outgrowth following MUP siRNA treatment when compared to a scrambled sequence control. Mice treated with streptozotocin (STZ) model features of human type 1 diabetic polyneuropathy, including decreases in multi-fiber motor and sensory measurements, and changes in thermal sensation in the extremities. To explore the potential role of MUP upregulation specifically in diabetes, we examined the impact of non-viral intranasal injection of MUP siRNA on indices of neuropathy in chronic type 1 diabetic mice. Following treatment, mice treated with MUP siRNA showed improvement in both motor and sensory nerve conduction velocities compared to scrambled controls. Taken together, this data suggests that MUP plays a growth-suppressive role in both diabetic and non-diabetic neurons and may also contribute to the electrophysiological and behavioral abnormalities associated with diabetic polyneuropathy. The repurposing of MUPs in sensory neurons identifies an interesting role for a supposed pheromone protein. [Supported by CIHR, CDA and ADI]

TRPV1 ACTIVATION BY CAPSAICIN ENHANCES THE REGENERATION OF SENSORY NEURONS

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Activation of small caliber TRPV1 ion channels is associated with intense sensory activation, whereas overactivation induces neurotoxicity. Subtoxic

activation of calcium influx into electrically activated neurons is associated with enhancement of their outgrowth properties (Singh et al, 2015). Here we asked whether similar activation, using low dose capsaicin, might similarly ramp up the regenerative activity of sensory neurons. Using rat adult primary sensory neurons, we identified a dose dependent relationship between capsaicin exposure and their outgrowth with enhancement at lower doses and expected neurotoxicity at higher doses. Doses that enhanced outgrowth were nonetheless associated with rises in intraneuronal calcium. We next tested whether a similar impact of TRPV1 activation *in vivo* might exist. We used a high sciatic crush injury mouse model to assess the impact of capsaicin at low (100uM) or high (1mM) doses applied directly at the site of axon outgrowth after injury. By 28 days following the single application of capsaicin, low doses of capsaicin showed more rapid recovery of thermal, but not mechanical sensation, whereas high dose capsaicin showed no significant difference compared to vehicle treated mice. In parallel with the neurotoxicity observed *in vitro*, the high dose capsaicin resulted in a decrease in sensory nerve conduction velocity, while the low dose showed no significant difference when compared to the vehicle treated animals. There was no impact on motor axon recovery. Taken together, subtoxic TRPV1 activation with intraneuronal calcium mobilization, as applied to regenerating sensory axons, enhances their outgrowth after injury, and improves behavioural recovery similar to that following extracellular electrical stimulation. [Supported by CIHR]

EFFECT OF PATISIRAN ON NERVE FIBER DENSITY AND AMYLOID CONTENT IN SKIN: RESULTS FROM PHASE 2 OPEN LABEL EXTENSION (OLE) STUDY IN hATTR AMYLOIDOSIS

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Hereditary transthyretin (hATTR) amyloidosis is a rapidly progressive, life-threatening disease caused by TTR gene variants, resulting in TTR misfolding and amyloid deposition in multiple organs, including peripheral nerves. hATTR amyloid polyneuropathy has prominent small fiber involvement characterized by neuropathic pain and dysautonomia. Measurement of intraepidermal and sweat gland nerve fiber density (IENFD, SGNFD) in skin biopsies has been useful in identifying small fiber abnormalities in hATTR. We report the effect of patisiran, an investigational RNAi therapeutic for the treatment of hATTR, over a 24-month period on IENFD, SGNFD and dermal amyloid content from the Phase 2 open-label extension (OLE) study. Skin biopsies (distal leg, distal thigh) were obtained every 6 months for up to 2 years within the Phase 2 OLE study (patisiran 0.3mg/kg IV, q3W, NCT01961921) and analyzed in a blinded manner by a central laboratory. All analyses are exploratory; nominal p-values are reported without adjustment for multiple testing. Twenty-seven patients enrolled; preliminary data indicated patisiran was generally well tolerated; resulted in sustained mean serum TTR lowering of ~80% for >24months and a mean 6.7-point decrease in mNIS+7 (n=24). Twenty-four patients underwent serial skin punch biopsies. At baseline, mean IENFD was 10.2 and 3.5 fibers/mm, while mean SGNFD was 6.8 and 3.8 m/mm^3 for distal thigh and distal leg, respectively. Amyloid was detected in ~80% of skin biopsies, mean baseline dermal amyloid content 10.9% and 15.8% for distal thigh and distal leg, respectively, which inversely correlated with IENFD and SGNFD. Overall, IENFD was stable throughout the 2-year treatment. SGNFD increased over time relative to baseline, reaching statistical significance at 6, 12, 18 and 24 months for distal thigh ($p<0.05$, all time points) and at 24 months for distal leg ($p=0.004$). Dermal amyloid content decreased over time and reached statistical significance at 6, 18 and 24 months for distal thigh ($p<0.05$, all time points) and at 6, 12, 18, and 24 months for distal leg ($p<0.05$, all time points). In summary, improvements in SGNFD and dermal amyloid content observed over a 2-year period suggest that these parameters have the potential to serve as biomarkers of response to patisiran treatment.

DIAGNOSTIC CHALLENGES IN AMYLOID NEUROPATHIES

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Misdiagnosis and delayed identification of an etiology for sensory neuropathies hampers adequate management and delays initiation of therapy. We present several cases that illustrate variable presentations of amyloid neuropathy (AN) and AN complicated by amyloid arthropathy.

A 59-year-old former college athlete developed painless difficulty walking. He was unable to keep up with family members during routine outings and subsequently was unable to navigate uneven ground during a hike, something he had previously excelled at. Balance decreased, making bicycling difficult. Neurological evaluation 12-months after symptom onset led to a diagnosis of peripheral neuropathy. A reversible neuropathy panel was normal though A1C was elevated (6.5%). Over several months, his strength/sensation deteriorated despite diet improvement, losing 20lbs and A1C improvement

(5.9%). Upon referral, EMG revealed a sensorimotor neuropathy with markedly reduced/absent sural, peroneal and tibial motor amplitudes. There was mild orthostasis. NIS was 84.
Skin biopsies revealed severe IENFD, SGNFD reductions and positive Congo red staining, confirmed with birefringence. A sural nerve biopsy confirmed amyloid deposits. Genetic testing revealed the TTR-FAP variant Leu58His. There was no history or suspicion for a family history of amyloid.
A 60-year-old male with a history of controlled diabetes x20 years developed abrupt onset of RLS 6 months after a lymphoma diagnosis. Treatment with rituximab led to radiographic resolution of the lymphoma though the patient developed progressive peripheral neuropathy confirmed by NCV/EMG. New-onset early satiety, mild orthostasis and ED emerged. Skin biopsies demonstrated a lichenoid pattern of amyloid deposition consistent with AA-amyloid.
A 72-year old woman with Leu58His TTR-FAP since 2002 developed progressive leg weakness, reduced ability to walk and low back pain. EMG demonstrated progression of her sensorimotor neuropathy and superimposed multilevel radiculopathy. Spine MRI demonstrated severe lumbar stenosis requiring surgical decompression. Postoperatively, she regained strength, walking more easily. Congo red staining of vertebral bone demonstrated widespread positive staining with birefringence consistent with amyloid arthropathy.
These cases illustrate to wide sprectrum of amyloid neuropathy presentation, an example of amyloid arthropathy-induced spinal stenosis and the utility of skin biopsy to diagnose and manage amyloid neuropathy.

HEREDITARY OR INFLAMMATORY CHILDHOOD NEUROPATHY – ELECTROPHYSIOLOGICAL ABNORMALITIES HELPFUL IN THE DIFFERENTIATION

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The differentiation between hereditary neuropathy and chronic inflammatory demyelinating polyneuropathy (CIDP) in children is especially significant because of completely different treatment possibilities and prognosis in these conditions. The aim of the study was to compare electrophysiological abnormalities in a group of children and young adults with demyelinating neuropathy of chronic or subacute onset.
Retrospective analysis of clinical and nerve conduction study (NCS) data included 3 children and 4 young adults with Charcot-Marie-Tooth Neuropathy X type 1 (CMTX1), 24 children with Charcot-Marie-Tooth Neuropathy type 1a (CMT1a) and 18 children with CIDP.
In our study 6/7 CMTX1 had both axonal and demyelinating changes in NCS study.
The AAN and EFNS electrophysiological CIDP criteria were fulfilled in 2/7 CMTX1, 23/24 CMT1a and 17/18 CIDP patients. Additionally 3 patients with CMTX1 are classified with EFNS criteria as “probable/possible CIDP”.
A distal compound muscle action potential (dCMAP) was >9ms in all CMT1a and 14/18 CIDP patients but none with CMTX1. Abnormal median/normal sural SNAP (AMNS) parameter was observed in 4//18 CIDP and 1/7 CTMX1 patients but not any CMT1a patient while abnormal sural/normal median SNAP (ASNM) parameter was found in 2/18 patients with CIDP. A difference between conduction velocities (CV) of two corresponding nerves >10 m/s was seen in 4/7 CMTX1 and 5/18 CIDP patients but no one with CTM1a.
One patient with CMTX1 had especially conspicuous difference between nerve conduction in lower limbs, with axonal neuropathy and demyelinating features, and upper limbs with no changes. One 3-years-old patient with genetically confirmed CMTX1 had no abnormalities in NCS.
Electrophysiological data of CMTX1, CMT1a and CIDP indicate diffuse demyelination, however in CMTX1 axonal changes coexist, seen in 6/7 patients, and asymmetrical abnormalities between corresponding upper and lower limb were observed in 4/7 patients.
Our study has showed that duration of dCMAP is useful not only in diagnosing an inflammatory neuropathy but also in differentiating CMTx from CIDP. However presence of the not homogenous abnormalities in NCS in patients with CMTx may mimic inflammatory neuropathy.

TESTING OVERWORK WEAKNESS IN CHARCOT-MARIE-TOOTH (CMT) DISEASE: IS IT TRUE OR FALSE?

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The overwork weakness (OW) problem in CMT disease has been debated for long time. It has been reported that the non-dominant hand (NDH) of patients with CMT disease is stronger than the dominant hand (DH) as a result of OW and some authors verified this hypothesis using MRC on different muscles (Van Pomeren, 2009). More recently, Piscosquito et al. (2014) found that the OW phenomenon does not exist using a dynamometer and the 9 hole peg test, a dexterity test.
We recruited 60 CMT patients and 60 healthy controls. We evaluated the strength of the 3-pinch and of the hand-grip with a dynamometer, the opposition ability with the Thumb Opposition Test (TOT) and applied an instrumental testing of hand function using the Sensor Engineered Glove Test (SEGT), which previously demonstrated its sensitiveness to measure severity of hands dysfunction in CMT patients.

TOT was significantly higher in the NDH compared to DH (NDH=8,23±1,60; DH=7,74±1,90, p<0.05) in CMT patients, instead there was no difference in DH and NDH in healthy controls. In the evaluation of 3-pinch and of the hand-grip, NDH performed slightly but not significantly better than the DH (3-pinch: DH=53,25±29,05 N; NDH=54,75±29,76 N; hand-grip: DH=57,81±31,11 N; NDH=62,36±32,20 N, p:ns). In normal controls we confirmed the 10% rule (Noguchi & Demura, 2009). Finally, SEGT results were similar between the NDH and DH in CMT patients but in normal controls there was a better performance in the DH.
In conclusion, this study supports the existence of the overwork weakness in CMT, evident in every measurements. Dexterity and overall ability of the hands impaired in the DH, probably because of compensating movements, compared with the healthy controls in the weaker hand. Finally, our results support the importance of avoiding supramaximal exercises and educating the CMT patients to prevent incorrect movements, which may overload the hand muscles.

FLAVIVIRUS ASSOCIATED GUILLAIN-BARRÉ SYNDROME IN SINGAPORE

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Antecedent infections that have been linked to Guillain-Barré syndrome (GBS) include Campylobacter jejuni, Haemophilus influenza, Epstein-Barr virus, Cytomegalovirus, Mycoplasma pneumoniae and Influenza A virus. In South- East Asia, the burden of mosquito-borne flavivirus infections is considerable. Even in a small country like Singapore, with a population of only 5.5 million and in spite of excellent sanitation and public health measures, dengue virus (DENV) infections can exceed 20,000 a year. Both symptomatic and asymptomatic DENV infections are associated with GBS. Zika Virus (ZIKV) infections were detected in Singapore in late August 2016. Doctors working in South-East Asia anecdotally report that GBS cases increase after rainy season when mosquitos breed. We are currently planning studies to estimate the hitherto unknown burden of GBS associated with DENV, ZIKV and other mosquito-borne viruses in this region. As a preliminary step, we reviewed the 27 GBS cases seen at our institution in 2016 for evidence of DENV and ZIKV. Three out of the 20 tested cases were positive for DENV serology. One of these 3 was also positive for DENV PCR. All these 3 patients had symptomatic dengue. Two had acute inflammatory demyelinating polyneuropathy (AIDP) and 1 acute motor axonal neuropathy (AMAN) subtype of GBS. None the 16 patients tested were positive for ZIKV PCR in serum and urine. One patient, with Miller Fisher syndrome (MFS), had serological evidence of recent ZIKV. He did not have clinical ZIKV symptoms. In 2 MFS cases, the initial detectable ZIKV IgG was later proven to be due to cross reactivity with previous DENV infection. In 3 cases (1 AMSAN, 1AIDP, 1 MFS) the initial ZIKV IgM was raised. We await analysis of convalescent sera to decide if they indeed had ZIKV or the results were related to previous and co-infection with DENV. Our preliminary findings indicate that flavivirus infections may account for at least some of the GBS cases in Singapore. The lack of symptoms in some cases and the interactions between ZIKV and DENV antibodies make accurate diagnoses challenging.

INVESTIGATION OF SELECTIVE HISTONE DEACETYLASE 6 INHIBITORS AS A TREATMENT FOR CHARCOT-MARIE-TOOTH DISEASE TYPE 1A USING A CO-CULTURE SYSTEM.

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Charcot-Marie-Tooth disease (CMT) is the most common inherited neurodegenerative disorder of the peripheral nervous system. It is divided into two main subtypes, a demyelinating subtype (CMT type 1) and an axonal form (CMT type 2). CMT is a length-dependent disease, in that it effects the longest neurons in the body, thus the muscles in the peripheral regions are affected first and foremost. Moreover, the majority of CMT patients share a classical phenotype with shared pathological hallmarks, such as distal muscular atrophy, reduction in nerve conductions, etc. but also molecular pathological hallmarks, like the breakdown in the transport of organelles and vesicles in neurons in a process called axonal transport.
Currently, there is no cure or effective treatment available to CMT patients. Histone deacetylase 6 (HDAC6) has been shown to be a key regulator in axonal transport. Moreover, inhibiting HDAC6 has been demonstrated to stabilize microtubules, which act as molecular tracks for motor proteins and facilitates axonal transport of cargos.
Our labs current focus is on CMT type 1A, the main cause of CMT, which is caused by a duplication of a segment of chromosome 17p11.2 containing the gene encoding peripheral myelin protein 22 (PMP22). PMP22 is mainly expressed by Schwann cells, the cells that myelinate neurons in the peripheral nervous system.
In the work presented, the commercial mouse Schwann cell-line, SW10 cells, was transfected to overexpress PMP22 using a lentivirus vector system to mimic that of CMT1A patient Schwann cells. The overexpression of PMP22 was confirmed using immunofluorescence and western blot techniques. These transfected SW10 Schwann cells were then co-cultured with primary mouse dorsal root ganglion neurons (DRGs) isolated from adult mice. These co-

cultures where then analysed after 3 weeks *in vitro* for axonal transport. The investigated groups were: a co-culture of DRGs + SW10 cells, a co-culture of DRGs + SW10 cells transfected with PMP22, and a co-culture of DRGs + a SW10 cell-line transfected with Green Fluorescent Protein using a lentivirus vector system, and a monoculture of DRGs. Furthermore, this work demonstrates that the overexpression of PMP22 in Schwann cells can impair axonal transport in co-cultured DRGs in comparison to the other co-culture groups. Moreover, these axonal transport defects were able to be rescued by the treatment of a HDAC6 inhibitor, Tubstatin A.
To conclude, selective HDAC6 inhibitors have been shown to be a beneficial treatment for a number of CMT subtypes in preclinical studies in our lab and offer as a viable treatment for a currently, untreatable debilitating disease.

CARPAL TUNNEL SYNDROME AS A HUMAN IN VIVO MODEL TO STUDY LARGE FIBER REGENERATION

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The observation of rate and patterns of cutaneous nerves regrowth after mechanical or pharmacological distal axonotmesis, has proven to be an excellent tool to study human nerve regeneration in normal and pathological conditions. Most of the observations, however, are referred to small fibers, possibly due to the availability of excellent models of reversible distal cutaneous small fiber axonopathy. No such model is available to study the regeneration of myelinated fibers in human. We studied regrowth of cutaneous large fibers in fingertip of patients with carpal tunnel syndrome after surgical decompression. We recruited 15 patients (M/F 4/11; age 46.9±8.8 years) with carpal tunnel syndrome candidate to surgery. Patients underwent clinical and electrophysiological evaluation, quantitative evaluation of discriminative threshold at 3rd fingertip. In the same site, patients also underwent 2mm punch skin biopsy. Skin sections were stained by immunohistochemical techniques and cutaneous innervation was analyzed by confocal microscopy. Meissner corpuscles and their myelinated afferences were assessed following previously published procedures. Twelve months after surgery, patients repeated functional evaluation and underwent a second skin biopsy two mm apart from the first one. Mean density of MCs/mm2 was 31.5±18.8 at time 0 and 34.2±17.7 at follow-up, mean density of myelinated endings was 24.4±14.0 at time 0 and 30.8±18.9 at follow-up. However, not in all patients regeneration occurred. Based on the variation of MC density between time 0 and follow-up we were able to identify patients in which active regeneration had occurred. In this subgroup mean density of MCs/mm2 was 23.1±16.6 at time 0 and 36.6±18.7 at follow-up ($p<0.01$) with a mean delta of +13.5. In the same group, mean density of myelinated endings was 18.6±13.4 at time 0 and 29.9±20.1 at follow-up ($p<0.01$) with a mean delta of +11.3. We describe morphological patterns associated to nerve regrowth in the biopsies of patients in which nerve regeneration occurs. We propose an in vivo model to study regeneration of large myelinated fiber endings in human skin. In addition to the count of nerve endings, the identification of patterns associated to nerve regeneration can increase the diagnostic yield of skin biopsy.

THE COMBINATIONAL DRUG PXT3003 IMPROVES NEUROMUSCULAR FUNCTION IN AN ANIMAL MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A DISEASE

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The most common type of Charcot-Marie-Tooth disease is caused by a duplication of *PMP22*, leading to dysmyelination, axonal loss and progressive muscle weakness (CMT1A). Currently, no approved treatment for CMT1A patients is available. Among others, preclinical therapeutic approaches aim to correct the *Pmp22* overexpression in order to ameliorate axonal loss and muscle weakness. We previously reported that the novel polytherapeutic drug PXT3003, a low-dose combination of baclofen, naltrexone and sorbitol, improved dysmyelination and axonal loss after long-term application in adult *Pmp22* transgenic rats, a known animal model of CMT1A. Interestingly, after short-term application in young CMT1A rats we observed a long-lasting prevention of muscle weakness as well but without obvious effects on dysmyelination and axonal loss. Improved distal motor latencies in the electrophysiological recordings and a shift in the axonal diameter distribution raised the hypothesis that therapy may improve the neuromuscular endplate pathology as another therapeutic target for CMT1A. Here, we report a preclinical trial in adult CMT1A rats treated from postnatal week 6 for 12 consecutive weeks as the most effective regimen in order to facilitate a deeper understanding of the mode-of-action of PXT3003. Long-term therapy effects were confirmed by an ameliorated behavioral phenotype, improved distal motor latencies and also nerve conduction velocity in the electrophysiological recordings. Histological analysis revealed an increased number of neuromuscular endplates, which were lowered to wildtype level after PXT3003

treatment. Further investigations include detailed analysis of peripheral nerve myelin thickness, internodal and nodal length, terminal axonal sprouting at the neuromuscular endplate and muscle fiber subtyping in treated CMT1A rats.

THE GERMAN CHARCOT-MARIE-TOOTH DISEASE NETWORK (CMT-NET): DISEASE SEVERITY AND PROGNOSTIC BIOMARKERS FROM BLOOD AND SKIN OF CMT1A PATIENTS

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Charcot-Marie-Tooth disease (CMT) is a rare hereditary neuropathy for which novel treatments are being developed and urgently needed. Only few clinical trials and natural history studies have been performed. Evaluation of intervention efficacy is hampered by slow progression and lack of sensitive outcome measures. The interindividual disease variability is high and prognostic disease measures are not established for CMT patients. Previously, we have identified skin-derived disease and progression biomarkers in a large European and US-based CMT1A cohort. Within the German Charcot-Marie-Tooth Disease Network (CMT-NET, www.cmt-net.de) we aim to establish easier accessible biomarkers in blood of CMT1A patients. Blood analysis is less invasive and can be repeatedly performed during clinical trials and routine patient care. We have started clinically assessing approximately 150 young, adolescent and adult CMT1A patients at 3 clinical centres (Münster, München, Göttingen) including a large set of clinical outcome measures (CMTNSv2, ONLS, 10MWT, 6MWT, Walk12, 9HPT, SF-36, FSS, PSQI, ESS, BDI-II). We will sample blood and skin tissue once a year at 0, 12 and 24 months for an observational period of 2 years. Tissue samples will be analyzed on the transcriptional, translational and epigenetic level. We envision that the diagnostic and progression biomarkers may be used to measure therapeutic effects within clinical trials and later in clinical routine monitoring. This is the first trial testing “circulating” biomarkers from blood in a prospective observational trial in CMT1A patients.

IGM ANTI-MAG PERIPHERAL NEUROPATHY: FROM PROPER ASSESSMENT TO TRIAL NEEDS (IMAGINE STUDY)

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IgM peripheral neuropathy is a slowly progressive and heterogeneous disease with symptoms ranging from mild foot numbness and minor imbalance to severe neuropathic pain and sensory and motor dysfunction. International consensus regarding assessment and treatment of patients with IgM peripheral neuropathy is lacking. This might be caused by the repeated use of suboptimal outcome measures, the small trial sizes with low numbers of treated patients, the indolent disease course needing a longer follow-up period to capture relevant changes, or the possibility that administered treatments were not aggressive enough. The IMAGiNe study is an international, multi-centre, prospective, observational cohort study, which will result in a unique collection of a large number of prospectively collected and highly standardized clinical data, and a biobank from a large population of well-defined patients with IgM peripheral neuropathy. The main objective is to describe in detail the variation in clinical subtypes, clinical disease course, past and current practice of treatment, antibody titres, and clinical picture at the various levels of assessing outcome. Patients being at least 18 years, and fulfilling the international criteria for IgM peripheral neuropathy are eligible. Exclusion is primarily based on concomitant diseases influencing peripheral nerve function. Several study parameters measuring weakness, sensation, activity and participation, ataxia, pain, and quality of life are of interest. In February 2017 an ENMC kick of meeting is organized, bringing together an IgM peripheral neuropathy study group. The meeting will focus on the development of a core set of outcome measures to be used in future studies in IgM peripheral neuropathy. The IMAGiNe study started in the Netherlands in September 2016, and to date 51 patients were included. The IMAGiNe study starts in the United Kingdom, Italy, and France in the beginning of 2017. Centres recruiting at least 10 patients with IgM peripheral neuropathy are eligible to participate in the study. During the PNS 2017 global recommendations from the ENMC meeting, as well as the first results of the IMAGiNe study, will be presented.

IVIG CAN INDUCE A RENAL IMPAIRMENT IN PATIENTS AT RISK WITH DYSIMMUNE NEUROPATHIES

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In dysimmune neuropathies patients (MMN, CIDP, GBS), IVIg have become the gold standard due to their efficacy and tolerability. Acute renal impairment, a rare but serious adverse event, can be induced by all IVIg. Its incidence is not determined precisely for each IVIg. It mostly occurs in patients at risk, with pre-existing conditions (prior renal insufficiency, diabetes, mellitus, arterial hypertension, elderly > 65 years old, dehydratation, hypervolemia, sepsis, paraproteinemia or concomitant use of other nephrotoxic drugs) and treated by immunomodulatory doses. As the number of these patients increases over the years, the choice of IVIg in association with the precautionary measures will be decisive to reduce or avoid the occurrence of this adverse event. From 1990s to 2000s, the nephrotoxicity of IVIg has been explained by tubular toxicity related to osmotic nephrosis. Sucrose, a stabilizer of some IVIg, has been implicated as one of the causes of this. Even if several new IVIg without sucrose are used, renal impairment cases have been described and studies have highlighted that sucrose is not the only IVIg stabilizer associated with tubular damage. However, in a recent study, renal impairment cases (4/5) have occurred in CIDP elderly patients treated by free-sucrose IVIg. The occurrence of renal failure seemed to be low (only 1/5) for patients treated with sucrose-IVIg in association with precautionary measures (hydratation, adaptation of dosage according body mass index, rate infusion). Otherwise, since 2010s, cases of renal impairment secondary to hemolysis have been increased with some IVIg but would be rare for full ethanolic fractionated products as they have been identified to generate very low occurrence of hemolysis. The occurrence of renal impairment related to IVIg seems to be multifactorial, need to find out all causes (mechanisms of different stabilizers, hemolysis, and concentration of IVIg). Registries would be helpful for physicians to define the incidence, relative risk of IVIg-related renal impairment and the right IVIg in association with precautionary measures in these patients at risk

CORRELATION BETWEEN ULTRA HIGH FREQUENCY ULTRASOUND (UHFUS) IMAGING AND HISTOLOGICAL FINDINGS OF SURAL NERVE IN CIDP

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The published ultrasound (US) studies on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) report diffusely increased cross-sectional area (CSA) of nerves. These data have not been correlated with histological patterns. To date, no further information about US ultrastructural nerve modification has been provided because of limited frequency range (10-20 MHz) of the US probe.
The aim of this preliminary study is to evaluate the correlation between histological findings from sural nerve biopsies and US patterns found with UHFUS (50 MHz) from sural nerve at the ankle.
Four patients with CIDP underwent UHFUS nerve evaluation of clinically affected sural nerve before undergoing a sural nerve biopsy. US findings included: cross-sectional area of the nerve, connective tissue depth and changes in echogenicity of fascicles. Those data were then compared to the histological findings obtained in transversal and longitudinal sections.
In all patients, UHFUS nerve changes were as following: CSA was increased; connective tissue was thickened and in two of the four patients hyperechogenicity of fascicles was observed. Also, thanks to the ultra-high-resolution of the probe, a direct correlation of the histological and US images was possible, so as a direct measurement of internal microstructure of the nerve.
UHFUS may be of adjunctive diagnostic value in CIDP assessment. More detailed images of sural nerve can be obtained compared with high-frequency US, allowing a better evaluation of the internal structure of the nerve. The increased CSA observed in all our subjects seems to relate to an enlargement of connective tissue, as confirmed by the histological study. In particular, we have observed a hyperechogenicity of fascicles in most severe patients; in those cases, histology confirmed an increase of endoneurial depth.
We speculate that those findings may explain a preliminary involvement of connective tissue in the pathogenesis of the CIDP; our findings of nerve enlargement may be tool to monitor disease activity in CIDP, and better understand disease pathogenesis. Further studies are needed to confirm these findings and additional data are being processed and will be presented during the meeting.

ULTRA HIGH FREQUENCY ULTRASOUND (UHFUS) NERVE IMAGING IN CIDP PATIENTS

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High-resolution ultrasound (hFUS, 20 MHz) of peripheral nerves is a valuable non-invasive, painless complement to neurophysiology, especially in the workup of CIDP. Nevertheless, the current spatial resolution of echographic images doesn't allow a detailed study of the nerves. Ultra-high frequency ultrasound (uhFUS, 50 MHz) is a new tool with a 3-5 times higher spatial resolution than traditional hFUS.

The aim of this preliminary study is to evaluate sensory and motor nerves structural characteristics found with UHFUS in patients with definite CIDP.
Seven patients with CIDP underwent uhFUS nerve evaluation of median, ulnar, peroneal and sural nerves, bilaterally. US findings included: cross-sectional area of the nerve, connective tissue depth, nerve vascularization and changes in echogenicity of fascicles. Patients also underwent electroneurography (ENG) and plexus MRI.
In all patients, uhFUS nerve changes were as following: CSA was increased; connective tissue was thickened. Two of the seven patients presented an epineural hypervascularization, observed at the Doppler evaluation; none of them was treated by iv immunoglobulines. Echographic changes were present even in the absence of MRI abnormalities (root hypertrophy). ENG characteristics correlated with the US patterns.
uhFUS may be of adjunctive diagnostic value in CIDP assessment. More detailed images of nerves can be obtained compared with high-frequency US, allowing a better evaluation of the internal structure of the nerve. The increased CSA observed in all our subjects seems to relate to an enlargement of connective tissue. In particular, uhFUS allows a more detailed study of nerves, demonstrating that the structural abnormalities hit connective tissue, while – conversely to previous studies – fascicles anatomy seems to be spared. We did not show nerve vascularization except in non-treated patients.
We speculate that those findings may explain a preliminary involvement of connective tissue in the pathogenesis of the CIDP; our findings of nerve enlargement may be tool to monitor disease activity in CIDP, and better understand disease pathogenesis. Further studies are needed to confirm these findings and additional data are being processed.

FUNCTIONAL CONSEQUENCES OF HIP DYSPLASIA IN PAEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

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6-20% of children with CMT are reported to have hip dysplasia. We aimed to investigate the relationship between radiological hip dysplasia indicators and walking pattern in children with CMT. Thirty children (15 female; 11.4±3.2yrs; 146±16.4cm; 44±18.3kg 21 CMT1A, 4 CMTX1, 2 CMTX3, 2 CMT1F, 1 CMT2A) underwent 3D gait analysis (3DGA), and had an anterior-posterior pelvis radiograph within 6 months of assessment. Radiographs were reviewed by two orthopaedic surgeons, and the reliability of 14 measures of dominant limb hip health via radiograph was assessed. Of the 14 measures, 8 measures had an intraclass correlation coefficient >0.75 between raters, and the more experienced surgeon's measures were used for further analysis. The 8 measures of acetabular index (AI), centre edge angle (CEA), neck shaft angle (NSA), medial joint space, head width, lateral uncoverage, migration percentage and triradiate were used to investigate correlations with kinematic and kinetic 3DGA variables of the pelvis and dominant limb hip, knee and ankle in 3 planes, temporal spatial parameters and Gait Profile Score. 3DGA data were captured with an 8-camera Vicon Nexus motion capture system using the lower body Plug-in-Gait model. Gait data were compared to 50 typically developing children (35 female; 9.8±3.8yrs, 140±19.6cm, 39±19.0kg). Five of 30 affected children had a migration percentage >20°, representing 17% of our sample. Maximum hip abductor moment in terminal stance was significantly lower than normative reference values, and was moderately correlated with 3 of the 8 radiographic measures (AI r=-0.52, p=0.023; NSA r=-0.50, p=0.006 and medial joint space r=-0.59, p=0.001). Walking speed (normalised to leg length) was correlated with medial joint space (r=0.51, p=0.004) head width (r=-0.68, p=0.0001) and triradiate (r=-0.51, p=0.004). Gait cycle percentage of double support correlated with medial joint space (r=0.56, p=0.001) head width (r=-0.78, p=0.0001) and triradiate (r=-0.63, p=0.0001). These results suggest evidence of a relationship between radiographic indicators of hip dysplasia and hip abductor function during gait in children with CMT.

CLINICAL AND ELETRODIAGNOSTIC FEATURES OF GANGLIONOPATHIES WITH SPECIAL REFERENCE TO ULNAR SENSORY-MOTOR AMPLITUDE RATIO(USMAR) FROM A TERTIARY CARE CENTER IN INDIA

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The ganglionopathies are a unique group of disorders with a varied etiology which includes autoimmune disorders, paraneoplastic syndromes and toxin induced causes. It has been observed that despite extensive investigations the cause of a sensory neuronopathy is often idiopathic in approximately 40-50% cases. Electrodiagnostic criteria to diagnose a possible ganglionopathy requires at least one sensory action potential absent or three sensory action potentials <30% of the lower limit of normal in the upper limbs plus less than two nerves with abnormal motor nerve conduction study in the lower limbs. Ulnar sensory-motor amplitude ratio values (USMAR) lower than 0.71 is useful in differentiating ganglionopathy from axonal length-dependent neuropathy.
We performed a retrospective analysis of 25 patients who were either admitted or evaluated in the outpatient department in Department of Neurology, Nizam's Institute of Medical Sciences**,** with a possible ganglionopathy as per the diagnostic criteria proposed by Camdessanche´ et al. Consecutive patients who sought treatment during a 5 year period

with a clinical pattern of sensory neuronopathy were analysed retrospectively. We reviewed the electrodiagnostic studies of patients and calculated the ulnar sensory-motor amplitude ratio values in comparison with 25 patients with a clinical and electrophysiological diagnosis of Diabetic axonal sensorimotor neuropathy.
The clinical profile of a ganglionopathy from the Indian subcontinent comprised of a prominent sensory ataxia as the initial presenting clinical manifestation with a predilection towards involvement of large-fiber sensory modalities. Electrophysiologically a pattern of absent SNAPs was characteristically encountered with a significant value of USMAR less than 0.7 , enabling differentiation from axonal length-dependent neuropathy.

CD1A AND CD1E GENE POLYMORPHISMS ARE NOT ASSOCIATED WITH THE SUSCEPTIBILITY TO GUILLAIN–BARRÉ SYNDROME IN BANGLADESH

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Guillain–Barré syndrome (GBS) is a post-infectious autoimmune polyradiculoneuropathy where immune response is triggered by molecular mimicry between glycolipid antigens expressed by an infective agent such as *Campylobacter jejuni* (*C. jejuni*) and human peripheral nerve gangliosides. CD1 molecules are MHC-like structures specialized in capturing and presenting a variety of glycolipids to antigen-specific T lymphocytes. The objective of this study was to investigate the possible role of coding region polymorphisms of CD1 genes in the pathogenesis of GBS in Bangladeshi population. Single nucleotide polymorphisms (SNPs) of exon 2 of CD1A (*1/*2) and CD1E (*1/*2) in 200 well defined GBS patients and 200 healthy controls were studied to delineate their effect in developing GBS. We genotyped exon 2 of both CD1A (cys/tryp) and CD1E (gln/arg) genes through PCR-RFLP. To validate these findings, direct sequencing of PCR product was performed for at least 10 samples for each position. We found no differences in genotypes and allele frequencies of both genes in GBS patients compared to controls. However, compared to control individuals with CD1A*2/CD1E*2 haplotype were 2.3 times more likely to develop GBS, whereas individuals with CD1A*2/CD1E*1 haplotype had a reduced relative risk by 4.3 times. A positive association of CD1A*2/CD1E*2 haplotype was observed only in axonal form of GBS (27.8% vs. 10.8%, p = <0.01). Haplotype CD1A*1/CD1E*2 was prevalent among anti-GM1 antibody positive GBS patient compared to anti-GM1 antibody negative patients (39.8% vs. 28.3%) though it was not statistically significant. SNPs in CD1A and CD1E were not associated with antecedent *C. jejuni* infection, disease severity and disease outcome at 6 months of follow up. In conclusion, CD1 polymorphisms are not a susceptibility or disease causing factor in GBS. Conversely, increasing knowledge of this field may offer new dimension for the research to elucidate better answer for disease pathogenesis and also contribute to conduct high power meta-analysis.

RECESSIVE SH3TC1 VARIANTS IN A CASE WITH PROGRESSIVE AND LETHAL PERIPHERAL DEMYELINATION

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Extensive genetic testing was performed on a unique patient, who received national media attention due to her severe CMT phenotype. The index patient was never able to walk independently, had difficulty breathing and swallowing and demonstrated aspiration by a barium swallow study. Nerve conduction velocity testing revealed velocities of 10 m/s in her upper extremity. She required continuous positive airway pressure (CPAP) for an upper respiratory infection and developed bilateral vocal cord paralysis. We used the combined Brief Assessment of Motor Function (BAMF) scale to evaluate her disability. Her fine motor scale was a 7/10, her upper extremity gross motor scale was a 6/10 and her lower extremity gross motor scale was 3/10. Unfortunately, she died at age 5 in her sleep, presumably from respiratory arrest. The proband's father was asymptomatic, however, his neurological exam showed pes cavus bilaterally and mild atrophy of the first dorsal interossei muscles in his hands. His nerve conduction velocities were slowed to 30 m/s in the upper extremities and his CMT neuropathy score (v2) was 9/36. We performed whole exome and subsequently whole genome sequencing in the trio. Comprehensive structural variant analysis for copy number variations, large deletions, and recombinations was completed by a combination of software tools. Known CMT genes were excluded as the underlying cause and the only viable candidate gene remaining was SH3TC1. We showed expression of SH3TC1 in peripheral nerve and Schwann cells. SH3TC1 is a paralogue to SH3TC2, which causes the recessively inherited dysmyelinating form CMT4C. Sanger sequencing confirmed the variants in our family, p.V41M (c.121G>A, chr4:8207042) and p.A1076P (c.3226G>C, chr4:8235184), and showed the segregation of the heterozygous variations. We hypothesize that the heterozygous paternal allele had a minimal effect and let to a very mild or subclinical form of peripheral neuropathy. Of interest, the recessive SH3TC2 gene has also been shown to

cause mild aberrant forms of peripheral nerve degeneration in carriers of heterozygous disease alleles. In summary, this paper will present genetic and molecular evidence from an extensive N=1 study proposing a novel CMT1 gene.

SCRENING OF HINT1 MUTATIONS ASSOCIATED WITH RECESSIVE AXONAL NEUROPATHY IN A BRAZILIAN COHORT

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Charcot-Marie-Tooth (CMT) is an important cause of morbidity worldwide. It is a heterogeneous disease manifesting as progressive weakness, wasting and loss of feeling in a length-dependent pattern. There are an increasing number of CMT-related genes in the literature. More recently, recessive mutations in the HINT1 gene have been reported as causative of predominant motor axonal neuropathy associated with neuromyotonic discharges on EMG. One of the characteristics of autosomal recessive CMT is it varying frequency in different populations and ethnic groups. We sought to evaluate the frequency of mutations in the HINT1 gene in a Brazilian cohort with axonal hereditary neuropathy. All patients included in this study born within South East area of Brazil. The group consists of consecutive patients with axonal neuropathy screened for recessive or sporadic axonal neuropathy in the Neurogenetics Laboratory of Clinical Hospital of Ribeirão Preto. Direct sequencing of the coding region of HINT1 gene was done. Among 100 patients screened, 98 were suspected of having recessive axonal neuropathy without neuromyothonic discharges, and two have axonal neuropathy associated with neuromyothonic discharges on EMG. We did not find any disease causing mutations among our patients. Some previously reported studies reported a high frequency of mutations in the HINT1 gene among recessive axonal neuropathies in some European countries. Our results demonstrated that frequencies of mutation underlying genetic hereditary neuropathies are different between different ethnic groups and have implications for the organization of services management of CMT, for genetic counseling, and for gene flow in different world populations.

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IN VITRO MORPHOLOGICAL STUDY OF BORTEZOMIB-INDUCED PERIPHERAL NEUROTOXICITY

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Bortezomib (BTZ) is a proteasome inhibitor widely used for multiple myeloma treatment. BTZ induced peripheral neuropathy (BIPN) is the most frequent adverse effect. BIPN in humans, is a dose dependent painful sensory neuropathy characterized by nerve axonopathy and a tendency to recover in the follow-up period after BTZ withdrawal. BIPN affects principally dorsal root ganglia (DRG) and different rodent models have shown alterations in sensory neurons, small unmyelinated axons, large myelinated axons, axonal mitochondria and Schwann cells. In this work, we evaluated the effects of BTZ *in vitro* on DRG neurons isolated from adult mice. Our interest focused on dystonin, a protein able to interact with all the three components of cytoskeleton (microtubules, microfilaments and intermediate filaments) and able to bind MAP1B (a MT-associated protein) through which can influence Golgi apparatus morphology. There are different neuronal isoforms of dystonin and in particular dystonin-a2 is able to modulate tubulin acetylation and stability through interaction with MAP1B. It is noteworthy to underline that MAP1B expression in the mature nervous system is restricted to sensory neurons. Western blot analysis demonstrated that a treatment with 10nM BTZ induces a statistically significant decrease in tubulin acetylation. This result does not go along with our previous study where we observed a tubulin polymerization increase after BTZ treatment. Therefore, we have decided to focus our interest on soma organelle organization that is well known to be dependent from cytoskeleton structure. Immunofluorescence images showed an altered distribution of acetylated tubulin in soma cytoplasm after 24 hour treatment. Moreover, confocal analysis of Cis Golgi (GM130) demonstrated that in BTZ treated neurons the normal Golgi structure is lost showing a spot-like non perinuclear labeling distribution. Additionally, dystonin distribution seemed comparable to that of cis Golgi apparatus suggesting that BTZ could induce a change in dystonin localization which in turn affects Golgi organization, probably through MAP1B.These data suggest that the cytoskeleton alterations, induced by BTZ, could probably cause wrong maturation and trafficking alteration of Golgi vesicles consequently impairing the correct sensorial function.

ATYPICAL CASE OF ACUTE MOTOR AND SENSORY AXONAL NEUROPATHY (AMSAN) IN A PATIENT CO-INFECTED WITH SYPHILIS

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Acute motor and sensory axonal neuropathy (AMSAN) is a clinical variant of Guillain-Barré syndrome (GBS) which has rarely been reported in

association with human immunodeficiency virus (HIV) and neurosyphilis. We describe a case of a 21-year-old woman who started with muscle weakness in the left leg followed by weakness in the right leg and in upper limbs in one month. Motor symptoms were followed by urinary and fecal incontinence. No preceding symptoms, as diarrhea or fever were referred. Neurological examination showed global areflexia with impairment of vibratory and tactile modalities, as well as loss of proprioception. Pinprick sensation was moderately compromised. No impairment of higher mental functions was observed. Other causes of neuropathies were ruled out. Cerebrospinal fluid (CSF) examination showed 0 cell/mm³, increased protein level, normal glucose level and negative VDRL test. Blood analysis showed HIV 1 and 2 positive serology tests, VDRL 1:16 and positive *T. pallidum* hemagglutination assay. IgM Cytomegalovirus antibody was negative, CD4 was in normal range and HIV load was undetectable. Cranial and spinal cord magnetic resonance imaging revealed extensive involvement of the posterior spinal cord tracts which supports the diagnosis of neurosyphilis. Nerve conduction studies showed a significant reduction in compound motor action potentials amplitudes, particularly at lower limbs, and absent sural nerve responses. Electromyography revealed positive waves and fibrillation at lower limbs. Treatment with methylprednisolone, human intravenous immunoglobulin and ceftriaxone has been settled, resulting in improvement of upper limbs paresis and sphincters dysfunction. Antiretroviral therapy was initiated. This AMSAN case is associated with central nervous system involvement, encompassing an encephalomyeloradiculopathyrelated to HIV/T. pallidum co-infection. *C.jejuni* is the main etiological agent associated with AMSAN, but there are some reports of HIV/CMV co-infected patients who presented this GBS variant. Facing a patient with AMSAN, mainly when CNS involvement is present, it is of crucial importance to undergo investigation of an ongoing infectious process, such as HIV and syphilis, considering the impact of early treatment on prognosis.

UPDATE ON THE INTERNATIONAL GBS OUTCOME STUDY IN CHILDREN (IGOS-KIDS)

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Only a few prospective cohort studies so far have investigated the clinical presentation and course of Guillain-Barré syndrome (GBS) in children using age-adjusted outcome scores. In 2015 we started a study based on the IGOS protocol but adjusted for children with GBS (IGOS-kids). (Pediatric)neurologists from Argentina, Australia and The Netherlands joined forces to determine the clinical and biological determinants of disease progression and recovery in GBS in children from different geographical areas. For each age category specific pain scales are used including the Comfort score for children < 4 years old, Pain faces revised age 5 - 12 years old and Numerical rating scale in children ≥ 12 years old and outcome measures. A new strength score was developed: GBS kids score. This score will be used and validated in addition to the MRC-sum score. The ONLS, R-ODS and FSS are also be used in IGOS-kids. Age-dependent quality of life questionnaires were added to the IGOS-kids protocol, namely the PedsQL and the PedsQL multidimensional fatigue scale. These scales are available for children ≥ 2 years old. An activity score validated for neuromuscular disorders for children ≥ 6 years old was also added. Currently there are 13 children included in IGOS-kids, eight children from Australia and five from The Netherlands. Additional clinicians and researchers interested in GBS in children are most welcome to participate in IGOS-kids.

PREDICTORS OF SEVERITY AND OUTCOME OF GUILLAIN-BARRÉ SYNDROME IN CHILDREN

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Prognostic models have been developed to predict the highly variable clinical course of Guillain-Barré syndrome (GBS) in adults. The clinical course of GBS is equally variable in children, but the current prognostic models have not been validated in children. In this study, we aimed to identify in children with GBS the characteristics at hospital admission that predict the clinical severity and outcome. The study was conducted in two patient cohorts from Europe: one (largely) German cohort of 265 children and one Dutch cohort of 140 children. Clinical information was obtained regarding preceding infection, first symptoms, neurological deficits at admission and nadir, results of additional investigations (cerebrospinal fluid and nerve conduction studies). Clinical severity, course and outcome was defined by the GBS disability score, especially the ability to walk unaided, at a follow-up of 1 month, 2 months, 3 months and 6 months after onset of symptoms. Univariate and multivariate regression analyses were performed initially on the two separate cohorts. Combined the cohorts

consisted of 405 children (age median 7 years, range 0-17 years) including 222 boys (55%). The median duration between onset of symptoms and hospital admission was 4 days (range 62). Pain at admission was remarkably frequent and present in 129 (71%) children. In the combined cohorts, 77 children (18.4%) developed respiratory failure and one child died. Multivariate regression analysis showed that in both cohorts strong predictors of respiratory failure available at hospital admission were cranial nerve involvement, a higher GBS disability score and a shorter period in days between onset of symptoms and admission. This information was used to develop and validate a prognostic model for children with GBS that will be presented at the conference. In conclusion, based on the analysis of two independent cohorts of patients the predictors of respiratory failure and clinical recovery were identified and validated. Similar factors were identified for adult patients, although the prognosis in children in general is better than in adults. This information will be used to develop a simple prognostic model for current clinical practice to predict the chance of respiratory failure and outcome in children with GBS.

PLASMA NEUROFILAMENT LIGHT CHAIN LEVELS ARE RAISED IN PATIENTS WITH INHERITED PERIPHERAL NEUROPATHY AND CORRELATE WITH DISEASE SEVERITY

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The negative trials of vitamin C in CMT1A have highlighted the lack of sensitive outcome measures in Charcot-Marie-Tooth disease (CMT). Neurofilaments are abundant neuronal cytoskeletal proteins and their concentration in blood is likely to reflect axonal breakdown. We therefore examined plasma neurofilament light chain (NFL) concentration as a potential biomarker in CMT. Blood samples were collected from 75 patients with CMT and 67 age matched healthy controls over a 1-year period. Disease severity was measured using the weighted CMT Examination and Neuropathy Scores. Plasma NFL concentration was determined using an in house developed Simoa assay based on the NFL antibodies from the NF-L light ELISA kit (UmanDiagnostics). Plasma NFL concentrations were significantly higher in CMT patients (median: 26.0 pg/ml; IQR: 17.3-33.6) than in controls (median: 14.6 pg/ml; IQR 11.0-21.1, $p<0.0001$) and correlated with disease severity as estimated by the weighted CMT examination (n=75, $r=0.43$, $p<0.0001$) and neuropathy scores (n=30, $r=0.37$, $p=0.044$). Concentrations were also significantly higher when subdividing CMT patients by genetic subtype; CMT1A (n=31, $p<0.001$), SPTLC1 (n=20, $p<0.001$) and GJB1 (n=11, $p=0.011$) or into demyelinating, CMT1 (n=48, $p<0.0001$) or axonal, CMT2 (n=27, $p<0.001$) forms compared to healthy controls. There was no significant difference in the plasma NFL concentration after 1 year in patients with CMT (n=9, mean difference -1.07 pg/ml, 95% confidence interval -8.2 - 6.0) or healthy volunteers (n=13, mean difference -1.2 pg/ml, 95% confidence interval 2.8 – 0.5) which is unsurprising as CMT is a slowly progressive disease in which the rates of axonal degeneration are likely to be constant and elevated. In summary, we have shown that plasma NFL levels are significantly raised in patients with CMT and that they correlate with disease severity. This is of relevance not only for the field of CMT but for peripheral neuropathies in general, and suggests that plasma NFL holds promise as a biomarker of peripheral neuropathy in both routine practice and clinical trials.

THE DIAGNOSTIC YIELD OF PCR-BASED CLONALITY TESTING ON NERVE BIOPSY IN THE DIAGNOSIS OF NEUROLYMPHOMATOSIS

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Neurolymphomatosis (infiltration of the peripheral nervous system by lymphoma cells) is a rare and usually devastating condition belonging to the spectrum of lymphoma-associated neuropathies. Cerebrospinal fluid examination with cytologic examination, flow cytometry and clonality testing by PCR may show malignant cells especially when nerve root involvement is prominent. However, nerve biopsy remains a useful tool to confirm the presence of malignant cells invading the nerve. Neuropathological features are important and PCR-based immunoglobulin or T-cell receptor clonality testing on nerve fragments may add notable value for the diagnosis of neurolymphomatosis, although this has not been systematically investigated. We retrospectively studied clinicopathological data and clonality results of nerve biopsy samples in patients with NL from 2 centres, performed between 2005 and 2016.

Among 16 patients with NL, we found 94% of B-cell lymphoma and one T-cell lymphoma. NL was the first manifestation in 62,5% of patients. The main clinical pattern was symmetrical progressive sensorimotor polyneuropathy in 38% of patients and pain was a prominent feature in 81%. Clonality testing showed a monoclonal rearrangement in 14 (88%) cases, oligoclonal rearrangement and no amplification in 2 (6%). The main histological pattern was perivascular

infiltration of predominant B-cells in the epineurium, without signs of vasculitis. The extent of axon loss was highly variable between patients. Various chemotherapeutic regimens were used and the median overall survival was 19 months. Only one case showed a monoclonal pattern among 22 control nerve samples from patients with other types of neuropathy including vasculitis and CIDP. Overall, we found that clonality testing on nerve biopsy specimens may provide decisive information on the presence of neurolymphomatosis, with a sensitivity of 87.5%, a specificity of 95.4%, a positive predictive value of 93.3% and a negative predictive value of 91.3%.
We confirm the utility of nerve biopsy for the diagnosis of NL and show the great yield of PCR-based clonality testing to assess the malignant feature of peripheral nervous system lymphoid infiltrates. Despite an accurate diagnosis, neurolymphomatosis still remains a devastating disease with an overall poor prognosis.

SMALL FIBER NEUROPATHY CHARACTERIZATION IN THE SOD1^{G93A} ALS MOUSE MODEL

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In the last years, cumulative data have shown that patients with amyotrophic lateral sclerosis (ALS) and mouse models of the disease present loss of small epidermal and dermal nerve fibers and sensory dysfunctions, in addition to the classical motor symptoms. Our objective is to characterize this small fiber neuropathy and to clarify if axonal loss involves all sort of fibers equally, or if there is some specificity. For this purpose, we performed an immunohistochemical characterization of total intraepidermal nerve endings (protein gene product; PGP9.5), peptidergic (calcitonin gene-related peptide; CGRP) and nonpeptidergical nerve epidermal endings (isolectin B4; IB4) of the SOD1^{G93A} mouse at different stages: presymptomatic stage (8 weeks), disease onset (12 weeks) and in symptomatic stage (16 weeks). The sympathetic sweat gland innervation was immunolabeled for vasoactive intestinal peptide (VIP) from very early stage (4 weeks) to disease onset (12 weeks). The results showed a marked reduction of the intraepidermal nerve fibers already in the presymptomatic stage compared to the wildtype littermates ($p<0.05$). This axonal loss affected more markedly the nonpeptidergic axons from the disease onset stage (39% axonal loss, $p<0.05$), whereas no significant differences were found in the CGRP positive fibers (14.3% axonal loss). A reduction of the sympathetic innervation of the sweat glands was also found from the disease onset stage (29% axonal loss, $p<0.05$). In summary, we have found that nonpeptidergic and sympathetic innervation of the skin are predominantly affected in the SOD1^{G93A} mouse model. These findings suggest that this specificity could be used as an accessible biomarker for the disease.

ARSENIC TRIOXIDE INDUCED PERIPHERAL NEUROPATHY: PROSPECTIVE EVALUATION OF TWO PATIENTS WITH ACUTE PROMYELOCYTIC LEUKEMIA

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Arsenic trioxide (ATO) is highly effective in treatment of acute promyelocytic leukemia (APL). It is licensed in Italy for treatment of relapsed-refractory APL and for first line chemotherapy in low risk patients. ATO most frequent side effects are well described, but less is known on ATO induced. We describe 2 APL patients who were treated with all-trans retinoic acid (ATRA)/ATO as first line therapy. The characteristics of ATO induced neuropathy was prospectically analyzed by neurological evaluation using both the total neuropathy score, clinical version (TNSc) (a validated scale for chemotherapy induced peripheral neuropathy) and neurophysiological assessment. Patients have been evaluated at baseline, at the end of the induction phase, at the end of ATO/ATRA treatment and 1 year after discontinuation of treatment. Baseline neurophysiology was performed at the end of induction phase. Both patients were men, respectively 41 and 53-yr-old. None of the patients had previous history of neuropathy. Baseline TNSc was 0 (no clinical signs of neuropathy) in both patients. Neurophysiological evaluation performed after the end of induction cycle did not reveal signs of peripheral neuropathy in both patients. Patient 1 received 387 mg of ATO during induction, total 1,040 mg. Patient 2 received 311 mg of ATO during induction, total 1,188. Both patients developed leg numbness during consolidation cycles and patient 1 also hand numbness. TNSc at the end of therapy was 1 in patient 1 and 3 in patient 2. Neurophysiology at the end of therapy detected signs of sensitive axonal neuropathy in both patients. They received full doses of ATO consolidation (0.15 mg/kg/day for 5 days/week, on alternate months for total 3 months and tretinoin 2 weeks on 2 weeks off). During the first year of follow-up both TNSc and neurophysiology 1 year after the end of consolidation cycle were consistent with full recovery. Our patients developed sensory axonal neuropathy during ATO therapy, that clinically manifested during consolidation cycles and improved up to complete recovery during follow-up. Published case reports show that outcomes may not be as good as in our patients. A multicenter prospective study evaluating the characteristics of ATO-induced neuropathy in APL is ongoing.

CHARCOT-MARIE-TOOTH NEUROPATHY MISDIAGNOSED AS CHRONIC INFLAMMATORY DEMYELINATING

POLYRADICULONEUROPATHY: A CASE SERIES.

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Hereditary and inflammatory neuropathies are peripheral nerve disorders of different pathophysiology whose identification is crucial for therapeutic approach. Diagnosis of CMT is easy when there is a family history, disease course is slowly progressive, neurophysiological findings are homogeneously abnormal. Cases of CMT1 patients with inflammatory-like phenotypes leading to a misdiagnosis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been described. The presence of “red flag signs”, such as slowly progressive decline, mild sensory symptoms, minimal electrophysiological progression and no response to therapy should prompt re-evaluation of the diagnosis of CIDP. The introduction of nerve neuroimaging has contributed to the diagnostic work-up. We describe 7 CMT patients (5 men, 2 women, mean age 58.6 ± 14.4 yrs, mean neuropathy duration 14.6 ± 8.9 yrs) with genetically confirmed CMT, who were initially diagnosed with CIDP. Neurophysiology showed demyelinating features in 5 patients, the remaining 2 patients had axonal features. CSF analysis showed albumin-cytological dissociation in 3 patients, oligoclonal IgG bands were present in 1 patient. Nerve ultrasound in 2 patients with demyelinating neuropathy showed diffuse increased cross-sectional area. MR-neurography in one patient confirmed diffuse nerve hypertrophy and increased signal intensity, supporting the hypothesis of a overlap syndrome. All patients were treated with immunomodulatory therapies. Among 5 patients with demyelinating features, 3 patients underwent IVIg for 6 months, without benefit; the remaining 2 were treated with steroids, showing temporary improvement. The 2 patients with axonal neuropathy complaining of a progressive history, underwent ex adjuvantibus plasma exchange and IVIg, without benefit. Given the lack of benefit from therapies, screening for hereditary neuropathies was performed. Among 5 patients with demyelinating neuropathy, 2 had CMT1A, 1CMT1B, 1CMT1D. Among the 2 patients with axonal neuropathy, one was diagnosed with CMT 2K. In 2 patients an overlap syndrome was present. Several clinical and laboratory features (CSF protein elevation), might contribute to the misdiagnosis of CIDP in CMT patients. Refractoriness to immune-modulatory treatment should rise the suspicion of a hereditary neuropathy. An overlap CMT/CIDP syndrome may be considered, in front of acute/subacute deterioration and/or proximal muscles involvement. Two patient with an overlap syndrome showed benefit after either steroids or IVIg.

FACIAL DIPLEGIA WITH BILATERAL FACIAL NERVE ENHANCEMENT AT 3T-MRI AND ANTI-GANGLIOSIDE ANTIBODIES.

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Facial diplegia is a rare regional subtype of Guillain-Barrè syndrome characterized by rapidly progressive bilateral facial palsy in absence of other cranial neuropathies, ataxia or limb weakness. The diagnosis is based on history, clinical examination, laboratory data. The outcome of this variant appears to be better than that of classical GBS. Although about 50% of GBS patients clinically exhibit facial nerve involvement, there are only few reports that demonstrate MRI gadolinium facial nerves enhancement. A 45-year-old previously healthy man sought neurological advice for the acute onset of right perioral paresthesias and hyposthenia at the extensor hallucis longus bilaterally. In the previous month, during a trip to China and Japan, he had suffered from gastroenteritis. At neurological examination he presented with bilateral extensor hallucis longus hyposthenia. Ankle jerk reflexes were absent. One week later, he developed bilateral facial palsy. Neurophysiology disclosed absence of activity in the facial nerves innervated muscles bilaterally and signs of mild partial denervation at right L5 metamer. CSF analysis showed increased protein levels (73 mg%) and 2.3 leucocytes/µL. Serological tests for infectious agents were negative and serum levels of Angiotensin Converting Enzyme were normal. Antibodies to monosialoganglioside GM1 of IgG isotype were positive (1/12800). 3T brain MRI showed, after gadolinium administration, marked bilateral enhancement of the facial nerves in their extra- and intra-canalicular segments. 3T lumbosacral MRI scan ruled out the presence of disc diseases as well as signal modifications within conus medullaris and cauda equine nerve roots. The patient was treated with IV immunoglobulins (0.4 g/Kg/die for 5 days) with benefit on facial weakness. At follow-up examination 2 months later, the patient presented a further improvement of the facial diplegia and neurophysiology disclosed a partial recovery of activity in the facial nerves, with persistent axonopatic damage. Bilateral extensor hallucis longus hyposthenia persisted. In conclusion, we report on a regional subtype of Guillain-Barrè syndrome with the curious association of facial diplegia and bilateral extensor hallucis longus hyposthenia, and IgG anti-ganglioside antibodies, that are not commonly described in facial diplegia. Moreover, we provide 3T brain MRI evidence of facial nerve involvement.

IMPAIRMENT OF MITOCHONDRIAL TRAFFICKING IN DORSAL ROOT GANGLION NEURONS IS DEPENDENT ON HYDROCARBON CHAIN LENGTH OF SATURATED FATTY ACIDS

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Diabetic neuropathy (DN) is the most common complication of diabetes affecting up to 60% of diabetic patients. The pathogenesis of DN in Type 2 diabetes is directly related to the metabolic syndrome associated with the western diet composed of elevated levels of long chain saturated fatty acids (SFAs) and low levels of medium chain SFAs. Long chain SFAs are associated with insulin resistance and dyslipidemia while medium chain SFAs have been associated with decreased lipid accumulation and improved mitochondrial function. Since DN is primarily a disorder of the sensory dorsal root ganglion (DRG) neurons, we sought to evaluate the impact of SFA hydrocarbon chain length on mitochondrial trafficking mechanisms that are critical for distributing ATP throughout DRG axon to provide energy for synaptic transmission. We hypothesize that SFAs with longer hydrocarbon chains will impair mitochondrial trafficking whereas medium length SFAs will not impact mitochondrial movement along the DRG axon. In this study, we examined the impact of SFA hydrocarbon chain length on mitochondrial trafficking, directionality and velocity in primary mouse DRG neurons. DRG neurons were treated with increasing concentrations of long chain SFAs, stearate and palmitate, or medium chain SFA, laurate, ranging from 31.25 to 250 micromolar for twenty-four hours. DRG neurons treated with long-chain SFAs, palmitate and stearate, showed a significant decrease in the percentage of motile mitochondria whereas medium chain SFA, laurate, does not alter mitochondrial motility. We next assessed whether motile mitochondria in DRG neurons treated with palmitate or stearate exhibited altered directionality or velocity of mitochondrial trafficking. Palmitate and stearate treatments resulted in a trending decrease in the number of mitochondria trafficking in both anterograde and retrograde directions. Furthermore, 62.5 to 250 micromolar palmitate and stearate induced a significant decrease in mitochondrial velocity. Laurate treatment, on the other hand, retained directionality and velocity of mitochondrial trafficking. These results suggest that hydrocarbon chain length of saturated fatty acids plays an important role in regulating mitochondrial trafficking mechanisms in dorsal root ganglion neurons. Impaired mitochondrial trafficking in DRG neurons exposed to elevated levels of long-chain SFAs may play a critical role in the progression of DN.

DIFFERENTIAL EFFECT OF SATURATED AND UNSATURATED FATTY ACIDS ON MITOCHONDRIAL TRAFFICKING IN DORSAL ROOT GANGLION SENSORY NEURONS

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Dyslipidemia is a critical factor that contributes to the development of diabetic neuropathy (DN). The progressive nerve damage associated with DN correlates with the dyslipidemic state characterized by elevated circulating levels of harmful saturated fatty acids (FAs) and low levels of beneficial unsaturated FAs. In DN, primary sensory dorsal root ganglion (DRG) neurons exhibit energy dyshomeostasis and mitochondrial dysfunction, however, little is known about the differential impact of saturated and unsaturated FAs on mitochondrial mechanisms in DRG neurons. Mitochondrial trafficking is an essential mechanism for transporting mitochondria throughout DRG axons to provide cellular ATP for neuronal function and neurotransmission. Since mitochondrial trafficking is regulated by metabolic flux, we sought to determine whether saturated FA, palmitate, and unsaturated FA, oleate, have differential effects on mitochondrial trafficking in DRG neurons. We evaluated mitochondrial trafficking patterns and the mitochondrial membrane potential (MMP) in primary DRG neurons treated with physiologically relevant concentrations of palmitate, oleate, and combinations of both FAs. Primary DRG neurons treated with 62.5 to 250 micromolar palmitate induced a significant and dose-dependent reduction in the percentage of motile mitochondria. These palmitate treatments also induced a dose-dependent reduction in mitochondrial velocity but did not impact the directionality of mitochondrial movement. Alternatively, 31.25 to 250 micromolar oleate treatments did not impair the percent of motile mitochondria, the direction of mitochondrial movement, or mitochondrial velocity. Since palmitate and oleate have differential effects on mitochondrial motility, we next assessed whether oleate could counter the inhibitory effect of palmitate on mitochondrial trafficking. Surprisingly, oleate/palmitate mixtures at ratios of 1:1 or 2:1 prevented palmitate-induced impairment of mitochondrial trafficking. We assessed the impact of palmitate and oleate on MMP by staining palmitate and oleate-treated DRG neurons with tetramethylrhodamine methyl ester. DRG neurons treated with 250 micromolar palmitate exhibited an increase in the percentage of depolarized mitochondria while mitochondria in oleate-treated DRG neurons retained MMP. Interestingly, DRG neurons treated with 1:1 oleate/palmitate mixtures also maintained polarized mitochondria. These results suggest that saturated and unsaturated FAs

have a distinct impact on mitochondrial trafficking mechanisms in DRG neurons and that equimolar ratios of oleate/palmitate can prevent impairment of mitochondrial trafficking.

SCO2 MUTATIONS CAUSE AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE

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Mutations in the mitochondrial copper-binding protein SCO2, cytochrome c oxidase assembly protein, have been reported in several cases of fatal infantile cardioencephalomyopathy with COX deficiency. We identified compound heterozygous variants in SCO2 in two unrelated patients with isolated length dependent axonal sensorimotor polyneuropathy of variable clinical severity (axonal autosomal recessive Charcot-Marie-Tooth disease type 4, CMT4) by whole exome sequencing. Although peripheral neuropathy has been described as a secondary feature in a few cases of fatal infantile cardioencephalomyopathy, the disease onset, clinical phenotype and survival in our patients differ significantly from the previously described cases. Our patients developed predominantly motor neuropathy; moreover, they are still alive and they have not developed cardiomyopathy, which is the main phenotype and cause of death at early infancy in reported patients. Both of our patients harbor mutations adjacent or near the conserved copper-binding motif (CXXXC), including the common reported pathogenic variant E140K and the novel change D135G. In addition, each patient carries a second mutation located in the same loop region of the protein, P169T and R171Q. Western blots from fibroblasts from these CMT patients showed reduced levels of COX2, a subunit of complex IV, indicating COX deficiency. Our findings demonstrate that CMT4 can be the predominant phenotype associated with SCO2 mutations, pointing to a broader phenotypic heterogeneity. The mechanism linking mitochondrial respiratory chain dysfunction to isolated axonal loss of variable severity remains to be elucidated.

MUSCARINIC RECEPTOR SIGNALING CONSTRAINS AXONAL OUTGROWTH BY AUGMENTING DISSOLUTION OF THE CYTOSKELETON IN ADULT SENSORY NEURONS

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The muscarinic acetylcholine (ACh) type 1 receptor (M_1R) is a metabotropic G protein-coupled receptor expressed by adult sensory neurons. Cholinergic signaling through muscarinic receptors can modulate axonal plasticity in invertebrates and lower vertebrates. We have recently shown that selective (pirenzepine) and specific (muscarinic toxin 7: MT7) M_1R antagonists elevate neurite outgrowth and protect from small and large fiber neuropathy in adult sensory neurons in various animal models (*Calcutt, et al., 2017*). Furthermore, we demonstrated that excessive cholinergic signaling due to M_1R overexpression caused a significant reduction in neurite outgrowth (*Calcutt, et al., 2017*). The mechanism of M_1R-antagonist driven neurite outgrowth remains poorly understood, however, we have proposed that ACh constrains axonal outgrowth via M_1R activation. Cholinergic signaling is mediated via recruitment of trimeric G proteins, of which G Alpha-12 and G Alpha-13 regulate cytoskeleton dynamics by control of tubulin polymerization. Activated GTP-bound G-Alpha proteins destabilize microtubules by increasing the intrinsic GTPase activity of tubulin. We have therefore tested the hypothesis that cholinergic signaling regulates neurite outgrowth via modulation of G protein mobilization and the dynamics of the tubulin cytoskeleton. We found that over-expression of M_1R in adult sensory neurons induced dissolution of the tubulin cytoskeleton in distal neurites. G Alpha-13 expression in adult sensory neurons was significantly higher ($P<0.001$, 7-fold) than G Alpha-12. Subsequent knockdown of G Alpha-13 in M_1R overexpressed sensory neurons significantly reversed the M_1R-induced reduction in relative levels of total neurite outgrowth (mean±SD: 347.96±190.12 (control) vs 545.40±321.97 (G Alpha-13 knockdown), $P<0.0001$, N=406 neurons). Further, treatment of M_1R overexpressing neurons with MT7 or pirenzepine sequestered G Alpha-12/13 proteins at the M_1R and significantly reversed the impaired cytoskeleton-mediated reduction in total neurite outgrowth (mean±SD: 895.9±172.9 (control), 1887±807 (+100nM MT7), 1706±507.5 (+1 micromolar pirenzepine); N=224, 230 and 198 neurons, respectively; for treated groups P value=0.0001 vs control by one-way ANOVA). MT7 and pirenzepine also significantly restored mitochondrial trafficking and abundance of mitochondria in the distal neurites. Our findings suggest a novel mechanism in which modulation of M_1R influences tubulin polymerization, mitochondrial distribution in nerve terminals and controls axonal outgrowth and regeneration. Funded by CIHR and NIH.

SELECTIVE MUSCARINIC RECEPTOR ANTAGONISM ACTIVATES THE ERK/MAPK PATHWAY IN ADULT SENSORY NEURONS

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Muscarinic receptors are a group of five G-protein coupled receptors (GPCRs) that are targeted by drugs for the treatment of several human pathophysiological conditions. We have recently shown that selective (pirenzepine) and specific (muscarinic toxin 7: MT7) antagonists of the muscarinic acetylcholine type1 receptor (M_1R) induced elevated neurite outgrowth and protected from small and large fiber neuropathy in adult sensory neurons in various animal models *(Calcutt et al., 2017)*. One of the major cellular effectors activated by GPCRs is extracellular signal-regulated kinase (ERK). The ERK signaling cascade regulates a variety of cellular processes including growth and proliferation. Both G protein and beta-arrestin mediated signaling pathways can lead to ERK activation by phosphorylation through different kinases. Activated ERK in turn can phosphorylate about 200 cellular substrates, thereby mediating diverse functions. In this study, we have analyzed beta-arrestin recruitment, as part of the receptor internalization process induced by agonist/antagonist binding. In addition, we studied phosphorylation of ERK by MT7 and pirenzepine using isoelectric focusing with phospho-ERK specific antibodies and a variety of cell-based assays including beta-arrestin and G protein (GNAS/GNASL/GNAQ/GNA11/GNA12/GNA13) knockout cell lines. Our study revealed that beta-arrestin is recruited to the M_1R upon MT7 and pirenzepine treatment. Treatment with 100nM MT7 and 1 micromolar pirenzepine significantly increased the dual phosphorylation of Tyr202 and Tyr204 residues of ERK1/2 in primary rat sensory neurons ($P<0.0001$) in comparison to muscarinic agonist carbachol (10 micromolar) and general antagonist atropine (50 micromolar). We have identified multiple distinct phosphorylation events on the M_1R by isoelectric focusing that are specific to MT7 and pirenzepine induction. Further, we have shown that MT7 and pirenzepine-mediated ERK phosphorylation is dependent on both G protein and beta-arrestin recruitment to M_1R. Finally, we reveal that increased ERK phosphorylation by MT7 and pirenzepine significantly ($p=0.005$ and 0.063, respectively) increased phosphorylation of cAMP responsive element binding protein (CREB) at Ser133. These results show for the first time that antagonists of the M_1R can activate the ERK signaling pathway and possibly drive phenotypic change in adult sensory neurons. Funded by CIHR # MOP-130282.

THE INHERITED NEUROPATHY VARIANT BROWSER

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Charcot-Marie-Tooth disease (CMT) is representative of inherited neuropathies affecting an estimated 1 in 2500 people. The immense advances in gene discovery gained from next-generation sequencing (NGS) projects have revealed the extent of CMT's genetic heterogeneity, with over 90 loci already identified. This knowledge is rapidly translated into clinical comprehensive gene testing panels, often containing over 100 genes. Such a large genomic space will invariantly yield variants of uncertain clinical significance (VUS) in nearly any person tested. This rise of the number of VUS creates major challenges for genetic counseling. In addition, less individual mutations in already known genes are being published as the academic merit is decreasing, and most such testing now happens in clinical laboratories. We propose to capture more of this data in the CMT field to gain a more complete collection of alleles in CMT genes, ideally in conjunction with detailed phenotypic data. This represents a rational approach to eventually reduce the number of VUS. Thus, we have created a unique, community-driven variant database for CMT researchers and clinicians. The Inherited Neuropathy Variant Browser provides simple, user-friendly access to currently reported CMT variation, including patient-level genotypic and phenotypic information. We have also designed an interactive rating system of genetic variation to assist the community with interpretation of VUS. For the initial release, we have collected genetic variation, along with genotypic and phenotypic data when available, from published literature, clinical lab reports, and our in-house database. We highly encourage new submissions of not only observed pathogenic variation, but also variation of unknown significance. The goal is to provide a platform for the CMT community to store, share, and discuss genetic data in order to resolve variation of uncertain significance as a joint-effort. With active participation, we aim to provide the community with a more complete mutational spectrum in CMT genes to assist allelic interpretation and patient diagnosis.

ABSENCE OF NEUROFILAMENT LIGHT CHAIN IN PATIENT-SPECIFIC MOTOR NEURONS IN AUTOSOMAL RECESSIVE CHARCOT-MARIE-TOOTH DISEASE

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Neurofilaments are strictly neuron-specific intermediate filaments crucial for maintaining axonal architecture. Pathogenic mutations in *NEFL*, which encodes the light chain of neurofilament, cause dominantly and recessively inherited Charcot-Marie-Tooth neuropathy (CMT). The *NEFL*-associated

neuropathy can be either axonal (type 2E) or demyelinating (type 1F). Most pathogenic NEFL variants are dominantly inherited missense mutations, which are thought to cause disease by inducing NEFL aggregation, leading to the disruption of axonal transport. However, investigation of disease mechanisms caused by the mutations has been complicated by the neuronal specificity of *NEFL*. We identified a homozygous *NEFL* variant c.1099 C>T predicting a nonsense change p.Arg367* in a patient with early-onset CMT. To elucidate the disease mechanism, we used pluripotent stem cells, reprogrammed from patient's skin fibroblasts, to differentiate patient-specific spinal motor neurons. The motor neurons revealed a near complete loss of NEFL mRNA, and absence of NEFL protein. Our results establish that NEFL is not essential for the development of human nervous system but its absence causes progressive axonal neuropathy. We currently profile the transcriptomic alterations of the motor neurons lacking NEFL using single cell RNA sequencing to identify compensatory pathways.

NERVE ULTRASOUND, MRI NEUROGRAPHY AND DIFFUSION TENSOR IMAGING ANALYSIS REVEALED PECULIAR NERVE ABNORMALITIES IN FRIEDREICH'S ATAXIA.

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Friedreich's ataxia (FRDA) is the most common autosomic recessive ataxia, due to a trinucleotide expansion within the Frataxin gene. Within the wide phenotype, FRDA patients present also with an axonal neuropathy whose pathological mechanisms are not completely known.
Eight patients (5 women, mean age 34.6 yrs, range 20-45) with genetically confirmed FRDA underwent neurophysiological and nerve ultrasound evaluation at four limbs bilaterally. Echogenicity and cross-sectional area (CSA) of median, ulnar, radial, peroneal, tibial, and sural nerves were recorded. MR neurography and diffusion tensor imaging (DTI) analysis were performed in one patient; fractional anisotropy (FA), radial (RD) and axial (AD) diffusivity of median, radial and ulnar nerve were calculated at proximal, intermediate and distal sites.
All patients presented with sensory axonal neuropathy. Seven patients (88%) presented with increased CSA of median and ulnar nerves at arm and axilla. Mean median nerve CSA at mid-upper arm was 20.9 mm^2 (normal values < 11 mm^2), mean ulnar nerve CSA at mid-upper arm was 13.6 mm^2 (normal values < 8 mm^2). Mean median nerve CSA at axilla was 13.8 mm^2 (normal values < 11 mm^2), mean ulnar nerve CSA at axilla was 9.9 mm^2 (normal values < 8 mm^2). MR Neurography (performed in one patient) confirmed diffuse swelling and signal hyperintensity of median and ulnar nerves at the arm and DTI analysis showed abnormal values of FA, AD and RD along the whole course of evaluated nerves thus suggesting a wide alteration of nerves structure.
FRDA patients presented with an axonal neuropathy characterized, at ultrasound, by a nerve enlargement strictly limited to mid-upper limbs in all patients, findings that cannot be solely explained by a dying-back axonopathy, as suggested by several authors. Neither a dorsal root ganglia neural loss could explain by itself our findings, because a diffuse CSA reduction would have been expected.
On the whole, these findings represent a peculiar feature in FRDA, but its pathophysiologic meaning remains unclear.

A BREED-PREVALENT CANINE MODEL OF LATE ONSET PERIPHERAL NEUROPATHY

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Inherited peripheral neuropathies are an important health concern for which there is currently no disease-modifying therapy. Dogs are affected by a variety of peripheral neuropathies that are breed-specific, indicating a strong genetic component. The use of in-bred populations, such as pure-bred dogs, is advantageous for genetic dissection of disease. Acquired peripheral neuropathy (APN) is an inherited late-onset generalized polyneuropathy with high prevalence in Labrador Retrievers. The most prominent features of APN, laryngeal paralysis and pelvic limb weakness, are associated with the longest peripheral motor nerves in the dog. The pathologic features of APN are similar to human peripheral neuropathy. Our aim is to understand the genetic and pathologic features of APN for development of this condition as a naturally occurring large animal model for human disease. We performed a genome-wide association study (GWAS) and short-read high-depth whole genome sequencing (WGS) to investigate the genetic underpinning of APN in the Labrador. Our GWAS data indicates that APN is an autosomal dominant disease. The initial analysis from the WGS study resulted in a potential causal variant with an autosomal dominant pattern; this variant is associated with an axonal gene. The neuropathologic progression and histologic features of APN are poorly defined. Using genetic markers from our GWAS study, we are able to confidently identify Labradors with pre-clinical APN, from which nerve biopsies can

be obtained. Preliminary analysis of biopsies from Labradors suggest APN is an axonopathy. Further histologic data from preclinical and symptomatic dogs is being obtained to further define the pathogenesis in this model. Defining the causal genetic variant(s) and understanding the pathologic features and progression of APN are necessary for the development of APN as a naturally occurring canine model of peripheral neuropathy.

GLOBAL TRANSCRIPTOME ANALYSES REVEAL A KEY ROLE FOR MORC2 IN THE AXONAL METABOLISM

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Mutations in *MORC2* lead to an axonal form of neuropathy (CMT2Z). To date, nine families have been published with mutations in the *MORC2* gene, showing that this gene is frequently involved in CMT. While the recent genetic data clearly established the causative role of MORC2 in CMT2Z, its phenotypic consequences in patients and role in neuronal biology remains to be clarified. Therefore, we aim to look for altered genetic and biochemical pathways with a transcriptomic approach in order to investigate the role of MORC2 in hereditary peripheral neuropathy. We have performed transcriptomic analysis using a human gene expression microarray (v3 8x60K, Agilent Technologies), in three HEK-293T cell lines: Control, MORC2 knock-down (Kd) and the overexpression of the most common MORC2 mutation, the p.R252W (NP_001290185) (Kr). Differential gene expression assessment was carried out using limma moderated t-statistics. Standard analysis techniques perform one test for each gene. Thus, for each gene, a t-test statistic is reported together with its corresponding p-value. In this analysis we have used the conventional multiple testing p-value correction procedures proposed by Benjamini Hochberg to derive adjusted p-values. The preliminary results reveals that Kd shows up-regulated genes involved in transmission of nerve impulse and cilium metabolism, suggesting that MORC2 might act at this level in the peripheral nervous system. Otherwise, Kr shows a major alteration of main axonal metabolic pathways, including the overexpression of genes related to the generation of neuronal action potential, transport through the axon and its targeting in synapse formation. Kr also shows a marked alteration of gene expression related to organization, assembly and cilium movement and with the axonemal dynein complex assembly. This study provides an important step towards understanding the pathomechanism underlying to MORC2 p.R252W and its role in CMT2Z. *Funds: ISCIII (PI15/00187) and Fundación Ramón Areces.*

THE AIFM1 p.F210S MUTATION CAUSES AN APOPTOTIC FAILURE AND ACTIVATION OF SENESCENT PROGRAM IN FIBROBLASTS DERIVED FROM PATIENT BIOPSIES

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AIFM1 encodes a mitochondria associated apoptosis inducing factor. Mutations in *AIFM1* lead to a wide spectrum of neurodegenerative disorders: Cowchock syndrome; a combined oxidative phosphorylation deficiency 6 (COXPD6) with severe encephalomyopathy; X-linked deafness with peripheral sensory neuropathy; spondyloepimetaphyseal dysplasia (SEMD) with mental retardation; and an infantile motor neuron disease. Previous studies showed severe defects in mitochondrial metabolism, related to redox function, mitochondrial fragmentation, and respiratory deficiencies. In addition, some mutations impair the protein expression of AIFM1 and cause an increase in caspase-independent apoptosis. By targeted next-generation sequencing, we detected the *AIFM1* c.629C>T (p.Phe210Ser), in a 12 year-boy. This mutation was confirmed in his 7 year-old affected brother. Electromyography and nerve conduction velocities studies revealed an axonal polyneuropathy with exclusive involvement of motor fibers, with an early childhood-onset. Both children currently show normal cognitive and cranial nerves functions. The *in silico* structural modeling of human AIFM1 showed that the mutation of a phenylalanine to serine at position 210 disrupts the hydrophobic interaction between Phe210 and Pro207, and consequently, it destabilizes an alpha-loop domain. Cartoon of protein superposition between two different human AIFM1 structures suggest that a lack of constraints in this region could affect the interaction between 517−533 helix and the 190−202 β-hairpin regions, a

very important stage for the functional activity of the AIFM1 protein. Patient-derived fibroblasts were used to investigate the pathological effect of the p.Phe210Ser mutation: fibroblasts from patients show a similar mRNA and protein expression of AIFM1 compared to healthy control fibroblasts. However, they have an aberrant morphology, from fibroblastic to polygonal shape, and they are larger than control fibroblast; mitochondria from mutant fibroblasts are markedly fragmented compared to controls; the viability of the patient's fibroblasts is lower, but it does not correlate with an increase in apoptosis. Instead, it seems to be caused by an increase in the expression of genes activating the senescent program, like P21 and P16. Our study confirms that variable effect of different mutations on the protein function may contribute to the clinical variability observed in AIFM1 patients. *Funds: ISCIII (PI12/00453); Fundació per Amor a l'Art.*

ESTABLISHMENT OF THE COCULTURE SYSTEM OF IMMORTALIZED SCHWANN CELLS *IFRS1* AND MOTOR NEURON-LIKE CELLS *NSC-34*

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Coculture models of neurons and Schwann cells have been utilized for the study of myelination and demyelination in the peripheral nervous system; in most of the previous studies, however, these cells were obtained from the primary culture with embryonic or neonatal animals. Because it is recognized that some biological properties of both neurons and Schwann cells change with maturation and aging, culture systems of adult animal cells appear to mimic peripheral nerve degeneration and regeneration better than those of immature animal cells. We have established spontaneously immortalized Schwann cell lines from long-term cultures of adult Fischer rat peripheral nerves. One of these cell lines, designated IFRS1, has been shown to retain distinct Schwann cell phenotypes, such as spindle-shaped morphology with expression of glial cell markers, synthesis and secretion of neurotrophic factors and cytokines, and fundamental ability to myelinate neurites in cocultures with adult rat dorsal root ganglion neurons and nerve growth factor-primed PC12 cells. Our current investigation focuses on the establishment of the coculture system of IFRS1 cells and NSC-34 motor neuron-like cells. NSC-34 cells were seeded at a low density (1 x 10^4/mL) and maintained for a week in serum-containing medium supplemented with non-essential amino acids and brain-derived neurotrophic factor (BDNF, 10 ng/mL). After overnight exposure to mitomycin C (MMC, 1 micro g/mL), NSC-34 cells were cocultured with IFRS1 cells (1 x 10^5/mL) and maintained in serum-containing medium supplemented with BDNF (10 ng/mL), ciliary neurotrophic factor (CNTF, 10 ng/mL) and coenzyme Q10 (1 micro M). Under this culture condition, overgrowth of NSC-34 cells was prevented and gradual movement of IFRS1 cells toward the neurites emerging from NSC-34 cell bodies was observed. Double-immunofluorescence staining carried out at day 28 of the coculture showed myelin protein zero-immunoreactive IFRS1 cells surrounding the beta III tubulin-immunoreactive neurites. This coculture system can be a beneficial tool to study the pathogenesis of motor neuron diseases (e.g. amyotrophic lateral sclerosis, Charcot–Marie–Tooth diseases and immune-mediated demyelinating neuropathies) and novel therapeutic approaches against them.

ACUTE TRANSIENT POLYNEURITIS ASSOCIATED WITH ZIKA VIRUS INFECTION

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Zika virus (ZIKV) is a flavivirus related to Dengue, Yellow Fever and West Nile viruses, and has been recently associated to the occurrence of neurological complications in children and adults. Previous studies have linked ZIKV to the development of Guillain-Barré syndrome (GBS), myelitis, meningoencephalitis and ophthalmological manifestations in adults. Guillain-Barré syndrome (GBS) encompasses a spectrum of post-infectious neuropathies characterized by different distributions of weakness and sensory impairment. Serum anti-ganglioside antibodies are often found and are related to different clinical patterns. Recently we have encountered patients in Rio de Janeiro, Brazil, with distal edema in lower limbs, acute weakness, pain and sensory disturbances during the acute stage of an acute febrile exanthematous illness. The symptoms persist for up to 7days, with complete resolution afterwards, without specific therapy. Blood concentrations of muscle enzymes show normal values, and electromyography and nerve conduction studies (EMG/NCS) are usually unremarkable. Of note, all cases have had positive RT-PCR for Zika virus, indicating an illness that occurred during the viremic phase of this arbovirus infection, and complete recovery within the expected timeframe for the resolution of the systemic viremia. There is a subset of patients who developed acute weakness very early after the initial viral symptoms, with clinical, laboratorial and electrophysiological findings that substantially differ from GBS. We describe three cases with similar features suggestive of an acute infective polyneuritis (AIPN). One might hypothesize that ZIKV might lead to a direct neurotropic injury, significant enough to cause weakness and sensory complaints, but not severe enough to cause permanent damage, resolving in conjunction with decreasing blood viremia. We consider that these patients differ from classical GBS because their illness begins during the acute febrile stage of an infective illness and the clinical course is more rapid leading to complete resolution in a few days.

A PEDIATRIC SERIES OF GUILLAIN BARRÉ SYNDROME INCLUDED IN IGOS PROTOCOL IN ARGENTINE

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Our objective is To describe a series of children with Guillain Barré syndrome (GBS) included in the IGOS protocol. As part of the IGOS multicenter protocol, pediatric patients meeting GBS diagnostic criteria, who consulted within the first 2 weeks of symptom onset and had parental consent to participate in the study were included. Patients were also offered to participate in the extended 3-year protocol. All patients were evaluated according to the IGOS protocol. Patients were recruited between October 2013 and June 2015. Twenty-four patients, eight girls, participated. Ages ranged from 6 months to 14 years (mean 5.8 years). All patients agreed to participate in the extended protocol, which was completed by 10 of them. Eight patients completed the 2-year follow-up and are still under evaluation. Five patients were lost to follow-up.Twenty-two had the classic variant of GBS and two Miller Fisher. Radicular pain in the back or lower limbs was reported by 70%. Twenty-three patients underwent lumbar puncture and albumin-cytological dissociation was found in 22. In all cases, CSF was stored for proteomic studies. All patients underwent EMG showing AIDP in 22, and AMSAN and AMAN in 1 each. One patient with AIDP developed to CIDP. In 13 patients full-spine MRI was performed and cauda equina enhancement was found in every case. Three patients required UCIP, two with invasive and one non-invasive ventilation. All patients were treated with gammaglobulin, with a second dose at 2 weeks in cases with a poor response. All 19 patients who followed the protocol were evaluated with the GBS disability score. Median score was 4 at baseline and between 0 and 1 at the 2-year assessment. We describe a series of children with GBS as a part of an international protocol including patients of different ages. Pain was a frequent and early symptom and could be determined despite the young age of our patients. Most patients fully recovered. We were invited to participate in IGOS KIDS to better assess this age group.

A DESCRIPTION OF GUILLAIN-BARRE SYNDROME IN LAO PEOPLE DEMOCRATIC REPUBLIC

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Laos People Democratic Republic is a country of 6.5 million people in South East Asia. Largely agricultural, its capital and metropolis is Vientiane. Adult neurological services are concentrated at Mittaphab Hospital, Vientiane serviced by three Neurologists. On the average about six cases of Guillain-Barré syndrome (GBS) are seen per year. It is believed that most patients do not seek medical attention. Cases appear to cluster during the rainy season. Most patients present late, often at the second week of illness when recovery is unapparent after seeking treatment from traditional medicine doctors and at district hospitals. A substantial number of patients seek treatment at hospitals across the border, in neighboring provinces of Thailand. Common antecedent symptoms are viral prodrome and diarrhea. Miller Fisher syndrome appears to be rare, possibly because of the mild deficits that do not prompt patients to seek medical attention. Diagnosis is made largely from clinical features and from spinal fluid analysis. Nerve conduction studies are not available. Patients are often treated with steroids by internists. Intravenous immunoglobulin and plasma exchange are not available. Common complications include pneumonia, autonomic dysfunction (fluctuating blood pressure), pressure sores and depression. Patients who develop respiratory failure are nursed at a twelve-bedded intensive care units. Plans are afoot to set up a prospective GBS database, systematically study antecedent infections, including of flaviviruses, and develop low-volume plasma exchange as a feasible therapeutic modality.

A GENE THERAPY APPROACH FOR TREATING CMT4C NEUROPATHY

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Charcot-Marie-Tooth Type 4C (CMT4C) is the most frequent form among recessively inherited demyelinating neuropathies and results from mutations in the *SH3TC2/KIAA1985* gene. *SH3TC2* mutations cause loss of function of the *SH3TC2* protein suggesting that gene replacement therapy may be useful for treating CMT4C. *Sh3tc2-/-* mice develop all major aspects of the human pathology including early onset progressive peripheral neuropathy with hypo- and demyelination along with decreased motor and sensory nerve conduction velocities, offering a relevant model for testing treatments for CMT4C. In order to develop a gene replacement strategy for CMT4C, we generated a novel lentiviral vector, LV-Mpz-*SH3TC2.myc*, to drive expression of the human *SH3TC2* cDNA under the control of the myelin protein zero (*Mpz*/P0) promoter specifically in myelinating Schwann cells. A C-terminus myc tag was included to facilitate expression analysis. A control vector (mock) was also produced in which the SH3TC2 cDNA was replaced by the EGFP reporter gene. We first confirmed expression of hSH3TC2 in Hela cells transfected with the pcDNA3-CMV-*SH3TC2.myc* vector. Immunofluorescence analysis confirmed a strong expression of SH3TC2 specifically at the plasma membrane with additional localization in a dotted pattern intracellularly. For *in vivo* gene delivery

we used both intraneural and intrathecal injections of the LV-Mpz-*SH3TC2.myc* vector in 2-week to 4-month old *sh3tc2-/-* mice. Expression of virally delivered h*SH3TC2* was assessed 4 weeks after injection. Immunofluorescence analysis showed hSH3TC2 immunoreactivity in perinuclear Schwann cell cytoplasm in sciatic nerve teased fibers of *sh3tc2-/-* mice following both intraneural and intrathecal delivery, while lumbar intrathecal gene delivery resulted additionally in expression of hSH3TC2 in the lumbar roots. Real time PCR analysis confirmed h*SH3TC2* mRNA expression in both lumbar roots and sciatic nerves. Thus, we have developed a novel lentiviral vector for Schwann cell targeted gene delivery to treat CMT4C and for testing possible therapeutic effects in the mouse model of the disease.
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SARM1 AND NAD INVOLMENT IN AXONAL DEGENERATION IN DEMYELINATING HEREDITARY NEUROPATHY CMT1A

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Hereditary neuropathies are a group of disorders which are characterised by the systemic impairment of peripheral nerves. More than 200 neuropathies are associated with causative gene defects [1]. Charcot Marie Tooth (CMT1A) neuropathy is the most frequent hereditary neuropathy, triggered by a mutation in the peripheral myelin protein gene 22 (PMP22). CMT1A leads to a primary loss of myelin sheath and afterwards to a degeneration of axons [2]. Symptoms appear with the degeneration of axons, whereas demyelination is thought to be largely asymptomatic. For that reason, we investigate in the mechanisms of axonal degeneration. For our analysis, we used purified axoplasma without detectable myelin proteins of the sciatic nerves of 20 weeks old PMP22-C61 mice. In this early stage of the axonal degeneration SARM1 was significantly increased. The NAD^+ concentration in the axoplasma was dramatically reduced. This correlates to the previous finding that SARM1 promotes axonal degeneration by cleavage of NAD^+. Additional studies showed an increase of the NAD^+-dependent axonal protective factor Sirt3 in PMP22-C61 sciatic nerves. NMNAT-1, known as the active component of the Wallerian degeneration slow gene, was unaffected in axoplasma of PMP22-C61 sciatic nerves.
Summarised, these results indicate that the pathway of SARM1, NAD^+ and Sirt3 may play a critical role in axonal degeneration in neuropathy.

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CMT2B2 IN CZECH PATIENTS WITH DIFFERENT GLAUCOMA PHENOTYPES AND THREE NOVEL SBF2 MUTATIONS, ONE OF THEM DE-NOVO

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Charcot-Marie-Tooth type 4B2 is a rare autosomal recessive, demyelinating neuropathy caused by biallelic mutations in the SBF2/MTMR13 gene. Only 19 pathogenic mutations were described since 2003, most of them truncating.
We report two unrelated Czech patients with CMT4B2, both sporadic cases in the family.
Patient 1 is a 27 year old man with congenital glaucoma after 8 ophthalmological surgeries. His early motor development was normal. At the age of 10 years parents noted gait problems, first neurological examination was at the age of 11 years, when EMG showed diffuse motor and sensory neuropathy with severely decreased NCV (22-29 m/s). He developed foot deformities (pes cavovarus) and underwent corrective orthopedic surgeries at the age of 16 years. After several DNA tests for demyelinating CMT the SFB2 gene was Sanger sequenced and a novel missense mutation p.Ile45Asn was found in homozygous state in the patient and in heterozygous state in both parents. The patient was later tested also by NGS of a panel of all 78 genes to be causal for hereditary neuropathies and no other potentially causal variants were detected.
Patient 2 is 35 years old man, with normal early motor development. At the age of 4 years parents noted gait problems with distal leg weakness which progressed into distal leg plegia at the age of 9 years. Hand weakness was noticed since the age of 10 years. He has severe atrophies of distal muscles of all extremities, is self ambulant. At the age of 25, EMG showed unrecordable responses from nerves of lower limbs and NCV was measurable only on ulnar nerve and was 13 m/s. At the age of 30 years increased intraocular pressure was diagnosed and he uses anti glaucoma eye drops. After many single gene tests for demyelinating CMT, we used NGS of a panel of 97 genes known to be causal for hereditary neuropathies and two novel heterozygous, probably pathogenic variants affecting invariant splice sites were detected: c.1601-2A>G and c.5232-10_5244del, both confirmed by Sanger sequencing. The first variant is also in the father, but the second is probably de-novo (not detected in parents, despite correct parentity).

DOPPLER ULTRASONOGRAPHY FINDING BETWEEN PRE- AND POST- OPERATION IN CARPAL TUNNEL SYNDROME

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Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy. Ultrasonography can be used to detect anatomic changes in CTS. More recently, it has been shown that Doppler ultrasonography can detect increased intraneural blood flow in CTS. The purpose of this study was to determine the most suitable finding of pre- and post-operation in CTS by ultrasonography. A total of 40 wrists of 25 patients with nerve conduction study (NCS) proven CTS were evaluated with ultrasonography. We measured the median nerve's cross-sectional area (CSA) and intraneural blood flow of median nerve by ultrasonography. The correlation between these ultrasonographic measurements, NCS severity and duration of clinical CTS symptoms was analyzed. The CSA (mean, 13 mm^2) was no significantly reduction after successful carpal tunnel release. Morphologic median nerve changes may persist for a longer period regardless of successful surgery and clinical improvement. However, intraneural blood flow is increasing after successful carpal tunnel release. We conclude that Doppler ultrasonography results strongly correlate with post operated CTS improvement. Hence Doppler ultrasonography is a useful method for functional improvement of pre- and post CTS operation.

ELECTRICAL STIMULATION AS A CONDITIONING LESION FOR PROMOTING PERIPHERAL NERVE REGENERATION

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The beneficial effects of a preinjury crush conditioning lesion (CL) on peripheral nerve regeneration is well-documented in animal models. No human studies have been attempted to date, given the ethical dilemma of deliberately injuring an intact nerve, and the difficulty in predicting the timing of a nerve injury. Recent studies demonstrate that 1 hour of electrical stimulation (ES) produces effects similar to CL in neuronal cultures. This, coupled with a surgical environment favoring nerve transfers, in which an intact nerve is deliberately cut to reinnervated a denervated muscle, means that ES may be clinically translatable to enhance regeneration. This study hypothesizes that ES prior to nerve injury will enhance nerve regeneration. Twelve Sprague-Dawley rats were divided into four groups based on conditioning-type to the mid-common peroneal (CP) nerve: ES (4), crush (4), sham-ES (2), and naïve (2). One week following conditioning, they underwent a cut/coaptation of the CP nerve at the sciatic trifurcation. Post-cut day 14, nerves and dorsal root ganglia (DRGs) were collected. Axonal counts of nerves stained with NF-200 revealed similar regeneration between ES and crush (3.2 vs. 3.8 mm, $p=0.6648$) that was superior to sham-stimulation (1.3 mm) or no-conditioning (1.0 mm, $p<0.05$). A greater number of axons at the distal tip were present in animals that received either type of conditioning compared to the unconditioned cohorts. DRGs were stained with neuronal injury marker Growth Associated Factor-43 (GAP-43), and satellite cell glial cells with Glial Fibrillary Acidic Protein (GFAP). Significant increase in GAP-43 expression at three days was observed in ES and crush cohorts compared to sham or naïve ($p<0.001$) cohorts. The satellite glial cells of ES and crush conditioning showed a significant increase in GFAP expression (29.3% and 39.3% respectively) compared to sham (8.6%) and naïve (13.5%) DRGs. By demonstrating similar improvements in axon regeneration, this proof of principle project suggests that ES conditioning may produce regenerative outcomes comparable to the classical crush injury model. In turn, this suggests that ES may be a promising method for delivering conditioning lesions in clinical trials for conditioning nerves prior to surgical intervention.

NEWLY DEVELOPED WALDENSTROM MACROGLOBULINEMIA DURING IMMUNOMODULATORY TREATMENT FOR ANTI-MAG ANTI-SULFATIDE CIDP

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We report a unique case of newly developed Waldenstrom's macroglobulinemia (WM) in a patient with chronic inflammatory demyelinating polyneuropathy (CIDP) with antibodies against myelin-associated glycoprotein (MAG) and sulfatide who was undergoing treatment with intravenous immunoglobulines (iv-IG). Subsequent Rituximab infusions did not have a positive impact.
Patients with WM can develop demyelinating and axonal polyneuropathies and few patients have anti-MAG and/or anti-sulfatide antibodies. Anti-MAG antibodies (4% of WM) are associated with sensorimotor axon loss and demyelination and anti-sulfatide (5% of WM) with sensory axonal loss. Rarely, both antibodies can be present, with a more severe clinical phenotype.
CIDP associated with anti-MAG and anti-sulfatide antibodies can represent independent entities, not associated with WM.
There are no reports to date of patients with CIDP associated with anti-MAG and anti-sulfatide antibodies that developed WM during immunomodulatory therapy with iv-IG. In addition, subsequent Rituximab infusions after the iv-IG were stopped have not been proven beneficial, as has been previously reported for anti-MAG CIDP patients.
Seventy-six year old right-handed gentleman presented with persistent numbness in his left foot, three months following artificial disc placement in his lumbar spine. Gradually he developed sensory ataxia. No radicular signs were present on exam or impingement on serial spine MRI's. NCS/EMG studies were consistent with a CIDP variant with severely prolonged distal motor latencies. Serum anti-MAG and anti-sulfatide antibodies were elevated. Chronic therapy with iv-IG was able to partially stabilize the symptoms; however, six years later he newly developed WM. Subsequent infusions

with Rituximab, after iv-IG was stopped, did not improve the clinical picture or the NCS/EMG findings. WM can newly develop in an autoimmune setting, such as CIDP associated with anti-MAG and anti-sulfatide antibodies. In this particular case, there was an ongoing immunomodulatory therapy for our CIDP patient, as he had monthly iv-IG infusions. This may reflect a possible induction of pathological B cell clone proliferation during the iv-IG treatment. Subsequent Rituximab infusions, after the iv-IG was stopped, did not improve the symptoms or the demyelination features on NCS/EMG. He continues to be symptomatic despite efforts.

THE GERMAN CHARCOT-MARIE-TOOTH DISEASE NETWORK (CMT-NET): FROM RISK FACTORS TO THERAPEUTIC ACTIONS

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Charcot-Marie-Tooth disease (CMT) is an inherited neuropathy without known cure (prevalance: 1:2500). Duplication of the gene encoding the peripheral myelin protein of 22kDA (PMP22) underlies the most common subtype CMT1A. Severely affected CMT patients suffer from sensory and motor symptoms with wheelchair-boundness. The clinical phenotype is highly variable and is determined by the amount of axonal loss, but the molecular mechanisms of the disturbed neuron-glia interaction are poorly understood. Risk factors have not been investigated. Therefore, CMT-NET, a German network funded by the German ministry of education and research (BMBF, Bonn, Germany) includes interdisciplinary expertise from molecular biology, neurology, neuropathology and human genetics in order to identify genetic and non-genetic risk factors of disease severity of CMT by: (i) examining the mechanisms of the disturbed axon-glia-interaction and neuronal vulnerability, (ii) identification of genetic modifiers and (iii) novel therapeutic targets, (iv) validating outcome measures in children and adults, (v) establishing a biobank and (vi) exploring the disease burden via an internationally harmonised patient registry. CMT-NET includes three service structures
CMT-NET will focus on CMT1A, but also includes rarer subforms. We will provide the scientific basis for the development of translational approaches to therapy in patients. Our approach bridges cutting edge molecular screening techniques, transgenic animal models of altered axon-glia interactions (fly, chick, mouse, rat), state-of-the-art genomic technologies and human patient trials in order to understand and treat the disease aggravation in CMT.

PERIPHERAL ANTINOCICEPTIVE EFFECT OF VENLAFAXINE IN RATS

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Analgesic effects of antidepressant drugs are well known for a long time, however, their systemic side effects limit their usage as an analgesics. Venlafaxine is an antidepressant drug that has different structure. Our purpose was to investigate whether systemic analgesic effect has been proved drug, venlafaxine, has local peripheral antinociceptive action. We applied vanlafaxine (25 µl 50, 100, 200, 400 µg) to male, Sprague-Dawley rats' paws by intraplantar injection and also by intraperitoneal route (5, 10, 20, 40 mg/kg) in formalin test, a model for acute and tonic pain. We also pretreated another groups of rats with 2 mg/kg naloxone (opioid receptor antagonist), 2 mg/kg CPT (adenosine A_1 receptor antagonist) or saline (ip.) before 200 µg/paw venlafaxine injection. To check the effect is local or not, we determined the blood levels of venlafaxine in at different time points after both the local and systemic applications by GC-MS method. Datas were expressed as number of flinches and total time for biting/licking of the injected paw over phase 1 (0–12 min) or phase 2 (16–60 min) and analyzed using the Student's t-test.
Venlafaxine induced antinociception at 100, 200 and 400 µg concentrations by the local peripheral application and at 20, 40 mg/kg doses by the systemic application in formalin test and the effects were comparable. Pretreatment with naloxone diminished the effect of venlafaxine in the both phases, however, it was not statistically significant. Pretreatment with CPT decreased venlafaxine induced antinociception only in phase 1. Neither naloxone nor CPT changed formalin induced nociceptive behaviors alone.
This is the first that determines the peripheral antinociceptive actions of venlafaxine in rat formalin test. with roles of opioid and adenosine A_1 receptors in this action. Our results suggest that venlafaxine has local peripheral antinociceptive effect and such an activity may led to trials for to use this drug as a cream-gel formulation for analgesia in clinics in the future. Topical application might permit the attainment of higher and more efficacious concentrations in the region of the sensory nerve terminal, with limited systemic side effects.

INCIDENCE OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY AND LONG TERM DISEASE BURDEN ON CANCER SURVIVORS IN A POPULATION-BASED COHORT

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CIPN is a common dose-limiting complication for patients with cancer. The long-term disease burden of CIPN is compounded by increasing cancer

survivorship, yet there are minimal data on long term outcomes following onset of CIPN, especially in population-based studies. We utilized the Rochester Epidemiology Project to examine incidence and disease burden of CIPN among individuals of Olmsted County, Minnesota with neurotoxic chemotherapy exposure between 2006 and 2008. Clinical records were queried for the presence of neuropathic signs, symptoms and ICD-9 diagnostic codes as well as for patient provided information on impairment with activities of daily living and use of pain medications. A total of 511 individuals with incident exposure to neurotoxic chemotherapy agents between 2006 and 2008 were identified. Based on AAN criteria for identifying peripheral neuropathy, 268 (54.4%) of these individuals were determined to have CIPN, while 241 (45.6%) controls did not. The median time from incident exposure to reported symptom onset was 71 days (IQR 28.5-122). Patients with CIPN received a neuropathy ICD-9 diagnosis in merely 37 cases (13.8%). Median survival following incident chemotherapy exposure among all cases and controls was 5.0 years with a significantly longer mean survival in cases with CIPN as compared to that of controls (6.4 years vs. 1.8 years, p<0.0001). In addition to acute effects in CIPN, individuals surviving greater than 5 years following exposure to neurotoxic chemotherapy continue to self-report increased symptoms of numbness (OR 2.8, 95% CI 1.6-5.2) and pain (OR 1.9, 95% CI 1.1.3.2) of the extremities. Through utilization of patient provided information, our study was able to collect data on long-term impairment associated with previous history of exposure to neurotoxic chemotherapy. Our results are consistent with previous reports of the high incidence of CIPN in the first two years following incident exposure. Additionally, our results provide evidence of high incidence of CIPN independent of individual chemotherapeutic agent used. Additionally, our results indicate ICD-9-CM diagnostic code attribution may dramatically underestimate the magnitude of CIPN. Increased survival following exposure to neurotoxic chemotherapy and its long-term disease burden necessitates further study of among survivors.

QUANTITATIVE MUSCLE ULTRASOUND AS A BIOMARKER IN CHARCOT-MARIE-TOOTH NEUROPATHY

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The utility of quantitative muscle ultrasound as a marker of disease severity in Charcot-Marie-Tooth (CMT) disease subtypes was investigated. Muscle ultrasound was prospectively performed on 252 individual muscles from 21 CMT patients (9 CMT1A, 8 CMTX1, 4 CMT2A) and compared to 120 muscles from 10 age and gender-matched controls. Muscle ultrasound recorded echogenicity and thickness in representative muscles including first dorsal interosseus (FDI) and tibialis anterior (TA). Muscle volume of FDI and thickness of TA correlated with MRC strength. Muscle echogenicity was significantly increased in FDI (65.05 vs 47.09; p<0.0001) and TA (89.45 vs 66.30; p<0.0001) of CMT patients. In TA, there was significantly higher muscle thickness (23 vs 18 vs 16 mm; p<0.0001) and lower muscle echogenicity (80 vs 95 vs 108; p<0.0001) in CMT1A compared to CMTX1 and CMT2A. This corresponded to disease severity based on muscle strength (MRC grading CMT1A vs CMTX1 vs CMT2A: 59 vs 48 vs 44; p=0.002). In CMT, quantitative muscle ultrasound of distal limb muscles is a useful marker of disease severity. The current findings suggest that quantitative muscle ultrasound has potential as a surrogate marker of disease progression in future interventional trials in CMT.

MODELING THE PATHOGENESIS OF CHARCOT-MARIE-TOOTH DISEASE TYPE 1A USING PATIENT-SPECIFIC IPSCS

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Charcot-Marie-Tooth (CMT) disease is the most frequent inherited peripheral neuropathy, and there is currently no available cure. The most common subtype of CMT, CMT1A, is completely associated with duplication of the PMP22 gene, which encodes peripheral myelin protein 22 of Schwann cells. Previous studies of CMT1A mainly relied on rodent models, and it is not yet clear how PMP22 overexpression leads to the phenotype in patients. Based on induced pluripotent stem cell (iPSC) technology, we herein developed a brand new in vitro cell model of CMT1A, called CMT1A-hiPSCs, in the hopes of simulating the developmental progress of the disease and gaining new insights into its pathogenesis. Here, we efficiently derived NCSCs from CMT1A-iPSCs and assessed the potential of the isolated CMT1A-neural crest stem cells (NCSCs) to differentiate into peripheral neurons and Schwann cells using defined media. We found that, unlike normal control NCSCs, CMT1A-NCSCs rarely

generated Schwann cells. Instead, CMT1A-NCSCs produced numerous endoneurial fibroblasts in the Schwann cell differentiation system. We further established a PMP22-overexpressing iPSC model, and obtained similar results when PMP22-NCSCs were subjected to Schwann cell differentiation. These results suggest that the development of Schwann cells in CMT1A patients is interrupted by the duplication of PMP22. With the exception of the demyelination-remyelination process, developmental disabilities of Schwann cells should be considered as an underlying cause of CMT1A.

CHARACTERISTIC OF RECOVERY FROM MUSCLE FATIGUE IN CHARCOT-MARIE-TOOTH PATIENTS WITH ELECTROMYOGRAPHIC STUDY (THIRD REPORT)

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Charcot-Marie-Tooth (CMT) disease is the most common hereditary motor and sensory neuropathy. Our preliminary report suggests that a certain CMT patient has the recruitment disorder of motor units during muscle fatigue and this disorder may be a factor of "super fatigability" in motor neuropathy patients. If the "super fatigability" occurs, we would expect patients with this characteristic to become slower in recovery from muscle fatigue than patients without this characteristic. In order to verify this hypothesis, we measured characteristic of recovery from muscle fatigue in Charcot-Marie-Tooth Patients with electromyographic study. Twenty three participants were asked to maintain their 75% of maximal voluntary isometric contraction (MVC) of elbow flexor until exhaustion as the fatigue exercise. In addition, the participants asked to perform 5s of their 50% of MVC at 30, 60, 90, 120, 180, 240, 300, 360, 420, 480s after the fatigue exercise as recovery tasks. The surface EMG (sEMG) signals of biceps brachii muscle were determined during the exercise and tasks. Muscle force, median power frequency (MdPF) and the root mean square of sEMG amplitude (RMS) were used as objective parameters of muscle fatigue. Borg scale was used as a subjective parameter of muscle fatigue. Six of twenty three participants showed significant decrease of RMS during the fatigue exercise. In consideration of this result, we compared alteration of MdPF in recovery task between six participants with decrease of RMS (abnormal group) and seventeen participants with increase of RMS (normal group). As the result, the abnormal group had at least 180s as the recovery time from muscle fatigue in contrast with 90s of normal group. The recovery time from muscle fatigue in subjective parameter was shorter than the time in objective parameters in each group. Our data support the "super fatigability" hypothesis. And that hypothesis may induce “hidden muscle fatigue”.

COMPARISON BETWEEN COMPLEX REGIONAL PAIN SYNDROME TYPE 1 AND 2 BASED ON ELECTROPHYSIOLOGIC, IMAGING AND CLINICAL FINDINGS

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Complex regional pain syndrome (CRPS) is a constant regional neuropathic pain characterized by various kinds of motor, sensory, and autonomic changes. Conventionally, the CRPS is divided into type I and II according to the absence and presence of nerve injury. But the pathogenesis of CRPS is not fully understood yet. And there is still no systematic comparative study between CRPS type I and II. We compared between CRPS type I and II using multimodal approaches including electrophysiologic, imaging, and clinical findings. The 171 patients (135 type I and 36 type II) diagnosed with CRPS using the International Association for the Study of Pain (IASP) diagnostic criteria were included. Type I and II were divided by electromyography and nerve conduction study. We obtained clinical information such as continuing pain, allodynia, hyperalgesia, edema, temperature, skin color, sweating, trophic change from patients. All patients were evaluated by bone scan, thermography, quantitative sudomotor axon reflex test (QSART), quantitative somatosensory test (QST). The ratio of QSART and temperature threshold abnormality in type II was higher compared to type I (85.7% vs 62.7%, 66.7% vs 46.3% respectively, P = 0.01 and 0.03), Among clinical symptoms, sweating change significantly high in type II compared to type I (77.8% vs 38.7%, P = 0.04). Other electrophysiologic and imaging, clinical findings were not significantly different in both type. In this study, we identified that CRPS type I and II are distinguished not only by the nerve injury but also by the sudomotor function, and QSART can serve as a good technique to differentiate between CRPS type I and II. It is estimated that there are two distinct pathogenesis in CRPS. Our results may be helpful to diagnose CRPS correctly and understand the pathogenesis of CRPS.

A CURIOUS CASE OF NUMBNESS, DIZZINESS, WETNESS, and DRYNESS – IS ROSS SYNDROME ON THE SPECTRUM OF SJOGREN NEUROPATHY?

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Sjogren Syndrome (SS) is an autoimmune inflammatory disorder of exocrine glands resulting in xerophthalmia and xerostomia. Ross Syndrome is a rare entity characterized by tonic pupil, hyporeflexia, and segmental anhidrosis. We present a 33-year-old Hispanic woman with debilitating sensory and autonomic neuropathies, and persistently elevated anti-SS-A and anti-SS-B antibodies, without the classic sicca complex. She initially developed diarrhea and an ear infection, then felt toe and later leg numbness, which eventually spread to her

cheeks and tongue, over few months. Four years later, her thumbs and index fingers started tingling. Also, she developed orthostatic lightheadedness, tachycardia, segmental hypohidrosis of the right abdomen, and hyperhidrosis of the remaining trunk, intermittent erythema, chronic diarrhea, and a 40-pound weight loss. Her exam demonstrated orthostatic hypotension, bilateral tonic pupils and light-near dissociation, sectoral palsy of the right iris sphincter, stocking-distribution diminished sensation to all modalities, pseudoathetosis, areflexia, dysmetria, intention tremor, Romberg, and sensory gait ataxia. MRI of neuraxis demonstrated T2-weighted hyperintensity in the dorsal spinal cord from C4 to the lower thoracic level, with mild atrophy. Electrodiagnostic testing was consistent with moderate-to-severe, length-dependent, asymmetric, sensory polyganglionopathies. CSF showed 6 oligoclonal bands. Serology showed elevated Antinuclear Antibody (1:1280, reference < 1:40), SS-A (148, reference < 20 U), SS-B (79, reference < 20 U), and Rheumatoid Factor (24, reference < 14 IU/mL) titers. The remaining workup was negative for infection (syphilis, HIV, HTLV, hepatitis, Lyme disease), paraneoplastic syndrome (anti-Hu and ganglionic nicotinic acetylcholine receptor antibodies), pyridoxine intoxication, malignancy (chest/abdomen/pelvis CT, breast ultrasound, axillary lymph node flow cytometry, colon and esophagus biopsy), celiac disease, vitamin deficiency, autoimmune disease (anti-aquaporin 4 and anti-GQ1b antibodies), and adrenoleukodystrophy. The patient received IVIg and steroid with some gait improvement and currently takes mycophenolate. Midodrine and fludrocortisone resolved her dizziness. This case highlights an important, treatable sensory ganglionopathy and systemic autonomic neuropathy due to Sjogren Syndrome, and illustrates the overlapping clinical triad of Ross Syndrome, which may guide future management.

REGULATORY B CELL FREQUENCIES INCREASE AFTER IVIG THERAPY IN INFLAMMATORY NEUROPATHIES.

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Inflammatory neuropathies are a heterogeneous group of peripheral nerve diseases that respond to immune-therapies. Chronic inflammatory polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) are two chronic inflammatory neuropathies responding to intravenous immunoglobulins (IVIg). B lymphocytes are involved in their pathogenesis. While widely used in clinical practice, IVIg's mechanism(s) remain not completely understood. IVIg are reported to lead to B-cell anergy and to increase regulatory T-cell function and frequency. Regulatory B cells (Bregs) are a rare subset of B lymphocytes that suppress immunopathology acting upon several target cells in the immune system. Impaired Breg yields have been described in a plethora of autoimmune conditions. The presence of regulatory B cells in inflammatory neuropathies and the effect of IVIg therapy on their frequencies has not been studied. The aim of this study is to describe the frequencies of Bregs in CIDP and MMN and the effect of IVIg on their frequencies. Patients fulfilling diagnostic criteria for CIDP or MMN and 14 matching controls were included. PBMCs were obtained by gradient centrifugation before IVIG infusion and one week after treatment. B-cells were isolated with negative selection magnetic beads, cultured and activated with the TLR9 agonist ODN and anti-human IgG+IgA+IgM. IL-10 secretion capacity was assessed by flow-cytometry. Twenty-eight patients were included of whom 20 where CIDP and 8 MMN. Of all patients included, 16 received IVIg and were suitable for pre and post IVIg Breg frequency comparisons. Breg frequencies did not differ in patients (before IVIg treatment) and controls ($p= 0.8518$, Mann Whitney test, Two-tailed). However, the frequencies of Bregs significantly increased one-week after treatment with IVIg ($p=0.0121$, Wilcoxon matched pairs test, Two-tailed). When stratifying by disease subtype, Breg frequencies increased in CIDP patients after IVIg ($p=0.0391$, Wilcoxon matched pairs test, Two-tailed) and in MMN ($p=0.1563$, Wilcoxon matched pairs test, Two-tailed) although results did not reach statistical significance in MMN. This is the first study that studies the Breg frequencies in CIDP and the first study that addresses the effect of IVIg on Breg frequencies. Our study provides the proof of principle that Bregs could become a biomarker for response to IVIg but this would need a larger and prospective study.

ANTIBODIES AGAINST CELL ADHESION MOLECULES AND NEURAL STRUCTURES IN PARANEOPLASTIC NEUROPATHIES

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Paraneoplastic neuropathies (PN) are rare, immune-mediated disorders of the peripheral nerve with important prognostic implications. Ectopical expression of neural antigens in the tumor leads to the development of onconeural antibodies. Several autoantibodies associate to PN, including anti-Hu, anti-CASPR2 or anti-CV2 antibodies but a significant proportion of PN lack identifiable antigens. Adhesion molecules that are autoantigens in other neuropathies, like contactin-1, are present in several

types of tumors. Our study proposes a systematic screening of autoantibodies against neural cell-adhesion molecules and neural structures to detect novel antigenic reactivies in PN.
Thirty-five patients followed in our centre and at the Neuroimmunology-Multiple Sclerosis Unit at Hospital Clínic de Barcelona, with PN fulfilling diagnostic criteria of possible (n=8; 22.9%) and definite (n=27; 77.1%) paraneoplastic disease were included. Serum samples were obtained and tested by immunocytochemistry against contactin-1 (CNTNT1), neurofascin 155 (NF155) and the CNTN1/CASPR1 complex. Primary cultures of dorsal-root ganglia (DRG) and rat Schwann cells were incubated with patients' sera to detect antibodies targeting neural structures. Ten individuals (28.6%) presented with a tumor and a neuropathy involving both sensory and motor symptoms. The remaining 25 patients (71.4%) presented with a tumor and a classical sensory neuronopathy without anti-Hu or any other onconeuronal antibody. Among the latter, 8 (22.9%) patients were diagnosed with Small-cell lung carcinoma. The rest of the 27 individuals (77.1%) associated diverse malignancies. We did not detect any sera reacting against CNTN1, NF155 or the CNTN1/CASPR1 complex. In IgG antibody screening experiments, 12 patients (34.3%) reacted against DRG neurons, 3 of them (8.6%) reacting strongly, and 3 patients (8.6%) reacted mildly against rat Schwann cells. In IgM experiments, 5 patients (14.3%) reacted slightly against DRG neurons and 11 patients (31.4%) against rat Schwann cells, 4 of them (11.4%) featuring strong staining. Experiments screening antibodies against motor neurons and immunoprecipitation assays are ongoing. Overall, 20% of patients reacted strongly against either neurons or Schwann cells. Our study did not detect antibodies against the neural adhesion molecules CNTN1, NF155 and the CNTN1/CASPR1 complex in patients with PN. However, a significant proportion of PN patients harbour antibodies targeting neural structures, which suggests that novel neoplasm-associated antigens remain to be discovered.

CHARCOT-MARIE-TOOTH DISEASE TYPE-1A (CMT1A) PLUS

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Objective: Despite of a shared genetic mutation of the trisomy of chromosome 17p12 (c17p12), patients with Charcot-Marie-Tooth type-1A (CMT1A) present with a high variability of their disease severities. The underlying cause for the variability is still unclear. In this study, we tested a hypothesis whether a second genetic mutation known to damage the nervous system is also present in CMT1A patients with early onset and severe phenotypes. **Methods:** From a cohort of 72 patients with CMT1A mutation (chromosome 17p12 duplication), we identified 11 patients with an early onset (< or = 5 years of age) of the disease. Four of the eleven also had DNA testing for a panel of 50 known CMT-related genes and sequencing of mitochondrial DNA in addition to the DNA testing for c17p12 duplication. **Results:** Besides the c17p12 duplication, we identified three additional mutations in the four patients with early onset. The mutations were a missense mutation of Arg67His in *MPZ* gene, an A10044G mutation in mitochondrial tRNA for glycin and a homozygous mutation of c17p12 duplication. Three of the four had symptomatic onset at birth. One showed symptoms at 3 years of age. Conduction velocities were severely reduced in all four patients (from 15 to 6m/s). **Interpretation:** Traditional approaches to identify genetic modifiers, including SNP association, assume that those modifiers are clustered in a small region of human genome and shared by the studied patients. However, our study suggests that genetic modifiers in CMT1A may be highly diverse and scattered throughout the genome, which could make the conventional approach via the genetic variants association difficult. Supported by grants from NINDS (R01NS066927) and the National Center for Advancing Translational Sciences (UL1TR000445).

PATTERN OF PERIPHERAL NEUROPATHY IN SJOGREN'S SYNDROME IN A TERTIARY CARE HOSPITAL FROM SOUTH INDIA

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Sjogren's syndrome(SS) is a systemic auto-immune disease that apart from exocrine glands may affect any organ. Involvement of peripheral nervous system results in wide spectrum of neuropathic manifestations. The Aim of our study was to evaluate the clinico-electrophysiological patterns and pathological characteristics of neuropathy in Sjogren's syndrome (SS) patients presented to neuromuscular clinic in a tertiary hospital from South India.**This is a retrospective study from the** Departments of Neurology, Rheumatology and Pathology from Nizam's Institute of Medical Sciences. Twenty one patients with diagnosis of SS and peripheral neuropathy between 2010 to 2016 were analysed. Clinical records, conventional nerve conduction studies, lip and nerve biopsy reports were collected.In 21 patients with SS associated neuropathy,male to female ratio was 2:1. In 14(66.7%) neuropathy was the initial manifestation,while in 4(20%)exocrinopathy preceded neuropathy. The patterns of neuropathy included mononeuropathy multiplex(MNM) in 7 patients (30%),ganglionopathy in 4 (20%),length dependant, trigeminal, autonomic neuropathy and CIDP in 2(10%)and cranial neuropathy in 1(10%).Eighteen(86%) were seropositive..Schirmer's test was positive in 13(61.9%).Nerve biopsy showed vasculitis in 5 patients, demyelinating and axonopathy in 2 patients each.We conclude that neuropathy is frequently the initial presentation of SS.MNM is the common pattern followed by ganglionopathy. Pattern of neuropathy helps in arriving at the diagnosis of SS. Confirmation

of SS is not by mere serology. Schirmer's test and lip biopsy are equally essential for the diagnosis especially in seronegative patients when clinical index of suspicion is high.

A NEW AUTOSOMAL RECESSIVE AMYELINATING CAUSE OF CHARCOT MARIE TOOTH DISEASE WITH CNS FEATURES AND RESPIRATORY DISTRESS

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Here, we report the first case of a human found to have a homozygous, presumed disease causing variant in the *ARL6IP1* gene, causing Charcot Marie Tooth disease (CMT) with central nervous system findings. The proband was born at term with Apgars of 3 and 9 at 1 and 3 minutes. He was found to have IUGR and was hospitalized for 9 days for weight gain. He developed respiratory distress during the admission and was intubated. Due to inability to extubate, he was transferred to Stanford Children's Hospital, where he remained for three months. Noted during admission was hypotonia, areflexia, minimal voluntary movment, sinus tachycardia, and dysautonomia. Brain MRI found polymicrogyria and cerebral underdevelopment with generally normal-appearing brainstem, with moderate ventriculomegaly. NCS found length dependent polyneuropathy with axonal degeneration. Follow up muscle and nerve biopsy found immature muscle and amyelinating neuropathy The patient had normal plasma amino acid, acylcarnitine, lactate, pyruvate, urine organic acid testing, opththalmology exam, newborn screen, and normal array CGH. Genetics ordered whole exome sequencing through Baylor Genetics Laboratory (Houston, TX, USA), which found a homozygous nonsense variant in *ARL6IP1* : c.346C>T, p.R116X. A second child had been identified by Baylor with two variants in this gene. That child had hypotonia, respiratory distress and seizures, and a muscle biopsy consistent with SMA. The parents of that child chose to withdraw care at 3 months of age. Our patient's parents continued with aggressive therapies, including tracheostomy and G-tube for feedings. He had several subsequent hospitalizations for respiratory distress, possible seizure activity, and buldging anterior fontenelle, but now, at two years of age, has made developmental progress and is living at home with his family. He is able to smile, reaching for toys and swatting objects. He has little voluntary movement, and no longer responds to light touch stimuli. Overall, this is the first picture of a child affected with a severe amyelinating form of CMT that causes weakness, hypotonia, and possible seizures, with the main concerning feature being the severe respiratory distress that may be life threatening, but can be managed with extreme care.

MONITORING PREGNANCY IN CHARCOT-MARIE-TOOTH DISEASE: RESULTS OF A SURVEY

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Charcot Marie Tooth (CMT) disease is the most common inherited peripheral neuropathy. Patients frequently ask whether pregnancy will affect their CMT, whether CMT will affect their pregnancy, the optimal delivery and whether they or their child will have a higher risk of complications during pregnancy or delivery. So far few studies address these questions. Currently no guidelines exist for the management of pregnancy, delivery and postnatal care in CMT patients.
The aim of the study is assess the impact of pregnancy on CMT and assess how CMT affects pregnancy, delivery and care of the new born baby.
We designed a retrospective questionnaire with expert help from an obstetrician with a special interest in pregnancy in patients with medical conditions.
The questionnaire is divided into four parts (prior, during, after pregnancy and delivery) and includes 29 questions on impairment, falls, pain, fatigue and respiratory complications during those periods; type of delivery, possible complications, details of anaesthesia and difficulties looking after the baby in the first months postpartum.
So far 48 women (85 pregnancies) with CMT and related disorders have answered the questionnaire. 50% of patients had CMT1A, the remaining had various subtypes of CMT and related disorders. Patients reported deterioration of CMT symptoms during pregnancy in 34% of pregnancies with resolution of symptoms after pregnancy in 52% of pregnancies. Of symptoms questioned walking (29%), balance (28%), and hand function (17%) deteriorated the most. There was an increased use of orthoses and walking aids during pregnancy. The majority of women (59%) had natural delivery, 17% were assisted and 28% had caesarian sections which was similar to the UK population (26%). No complications with anaesthesia were reported.
The survey is currently ongoing. We plan to survey 100 consecutive patients. Data acquired from this survey will provide valuable information on current practice and will inform future guidelines and standard of care in Charcot Marie Tooth disease.

CMAP SCAN ANALYSIS IN MULTIFOCAL MOTOR NEUROPATHY

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Multifocal motor neuropathy (MMN) is a slowly progressive disorder in adults, characterized by asymmetrical limb weakness, mainly affecting the arms. Despite beneficial effect of immunoglobulins, weakness gradually progresses. A major determinant of muscle weakness is the degeneration of affected motor axons. Treatments aiming to reduce loss of motor axons require objective tools to quantify such

an effect. Therefore, we applied the compound muscle action potential (CMAP) scan, which is an electrophysiological method that, with increasing transcutaneous stimulus-currents, successively activates all motor units (MUs) in a muscle. It captures the contribution of enlarged MUs due to reinnervation by the presence of relative large discontinuities in the scan. The aim of the present study was to identify pathophysiological changes of MU-loss and reinnervation in MMN patients by means of the CMAP-scan. Recordings were obtained from 12 MMN patients. CMAP-scan recordings were performed in the median nerve at the wrist where motor responses were recorded from the thenar muscle. We determined the number of largest CMAP-scan discontinuities by means of a novel marker, D50, where a low number is indicative of MU-loss and enlarged MUs. Furthermore, we applied the recently developed method of professor Hugh Bostock for obtaining a MU-number estimate from the CMAP-scan. The median peak CMAP amplitude was 7.6 mV (range 3.2 – 12.1 mV) and median D50 was 43 (range 12 – 54). In three MMN patients with a normal maximum CMAP amplitude (> 5 mV) a reduced D50 (< 25) was found indicative of MU-loss and enlarged MUs. Furthermore, D50 and the estimate of MU number were significantly related ($r = 0.85$, $p < 0.001$, $n = 12$). The findings suggest that the CMAP-scan is a sensitive tool in detecting the underlying pathological changes of reinnervation and MU-loss in MMN, more so than standard maximum CMAP amplitude. It is quick and easy to perform and has the potential to be useful for follow-up studies.

RESPONSIVENESS OF CORNEAL CONFOCAL MICROSCOPY TO DIABETIC NEUROPATHY PROGRESSION

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Corneal confocal microscopy (CCM) directly and quantitatively assesses corneal innervation including nerve fiber length (NFL) and density (NFD). CCM has shown promise as a diagnostic test. We have previously demonstrated that CCM has a diagnostic performance for diabetic neuropathy (DPN) similar to skin biopsy with assessment of intraepidermal nerve fiber density (IENFD) and nerve conduction studies (NCS). The responsiveness of these surrogate measures to DPN progression and their relation to clinically meaningful outcomes has not been well explored. 144 diabetic patients undergoing annual retinopathy examination were recruited. Each underwent CCM, IENFD, NCS including sural sensory and peroneal motor responses, the Utah Early Neuropathy Score (UENS), the Norfolk Quality of Life – Diabetic Neuropathy (NQOL-DN, a validated neuropathy specific QOL scale), and a 6 minute walk test (6MWT). 55 with DPN based on symptoms (82%) or signs underwent repeat testing at 9 months and 35 at 18 months. At baseline, NQOL-DN correlated with sural sensory amplitude (SSA) (-0.295, $p<0.0004$), peroneal motor conduction velocity (PCV) (-0.466, $p<0.0003$) and IENFD (-0.317, $p<0.001$). No CCM metric was related to QOL. 6MWT distance correlated with SSA (0.320, $p<0.0002$), NFL (0.250, $p<0.0038$) and NFD (0.217, $p<0.0124$). Over 18 months, there was a significant worsening in DPN signs assessed by the UENS (increase 1.43 +/- 0.65, $p<0.037$). SSA declined 0.78 uV ($p<0.079$) and IENFD 1.8 fibers/mm ($p<0.063$). There was no change in any CCM metric, PCV or NQOL-DN. These findings suggest measures of distal axonal integrity are most sensitive to neuropathy progression, with IENFD having the greatest responsiveness. In contrast, CCM was not responsive to DPN progression. Both NCS and IENFD (but not CCM) were significantly correlated with neuropathy-specific QOL, whereas NCS and CCM measures correlated with physical functioning. The responsiveness of IENFD and SSA, and their relationship to QOL support their selection as endpoints in DPN clinical trials.

INTERLEUKIN 10 DEFICIENCY PARADOXICALLY PROTECTS FROM SPONTANEOUS AUTOIMMUNE PERIPHERAL NEUROPATHY IN A MOUSE MODEL OF CIDP

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Chronic Inflammatory Demyelination Polyradiculoneuropathy (CIDP) affects 1 in 10,000 people, and is marked by chronic autoimmune infiltration of peripheral nerves and destruction of the myelin sheath. With current therapies, only 26% of CIDP patients achieve complete remission. To produce more effective, mechanism-based therapies, we study mice with a partial loss of function G228W substitution in the Autoimmune Regulator (Aire) gene on the non-obese diabetic (NOD) background (NOD.Aire$^{GW/+}$) that develop spontaneous autoimmune peripheral polyneuropathy (SAPP) resembling CIDP. Autoimmunity can result from defective immunosuppression. The potent, immunosuppressive cytokine interleukin 10 (IL-10) is increased in the peripheral blood mononuclear cells (PBMCs) of active phase CIDP patients relative to remission phase patients. Further, PBMCs from CIDP patients produce IL-10 in response to the myelin protein P2. Despite these findings, whether IL-10 is important for CIDP pathogenesis is not known. Thus, we sought to determine the role of IL-10 in SAPP. IL-10 was highly upregulated in sciatic nerves of NOD.Aire$^{GW/+}$ mice with SAPP, suggesting it may play an immunosuppressive role in pathogenesis. However, genetic ablation of IL-10 in NOD.Aire$^{GW/+}$ mice lead to a paradoxical delay in disease development. Age-matched IL-10-deficient NOD.Aire$^{GW/+}$ mice exhibited no sciatic nerve infiltrate and no reduction in nerve conduction during electrodiagnostic studies. Interestingly, the delay in SAPP was specific, since the incidences of five other autoimmune manifestations in IL-10-deficient

NOD.Aire$^{GW/+}$ mice were unchanged relative to IL-10-sufficient NOD.Aire$^{GW/+}$ controls. Importantly, IL-10-deficient NOD.Aire$^{GW/+}$ mice did not have colitis, which is consistent with previous studies of IL-10 deficiency on the NOD background. IL-10 is known to perform effector functions in autoimmunity by promoting B cell secretion of immunoglobulins. However, genetic ablation of B cells did not affect neuropathy development in NOD.Aire$^{GW/+}$ mice, suggesting B cells are dispensable for pathogenesis and unlikely to mediate the protective effect of IL-10 deficiency. IL-10-deficient NOD.Aire$^{GW/+}$ CD4+ T cells, which are sufficient to transfer SAPP, exhibited increased activation, increased interferon gamma secretion, and preserved nerve-specific T cell activation. These data suggest T cell activation and priming are unperturbed and not the mechanism of protection. In summary, our data showed that IL-10 was paradoxically an effector cytokine in SAPP.

MARKED DECREMENT IN CMAP AMPLITUDE FOLLOWING PROLONGED EXERCISE IN SECONDARY HYPOKALEMIC PARALYSIS

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Long exercise test (LET) has been used especially in myotonic syndromes and muscle channelopathies. Marked decrement in compound muscle action potential (CMAP) amplitude after prolonged exercise was previously reported in patients with paramyotonia congenita, hyperkalemic or hypokalemic periodic paralysis. We describe a patient with secondary hypokalemic paralysis who showed abnormal LET results. A 43-year-old man presented with ascending flaccid paralysis which evolved in a hyperacute fashion. The patient became quadriplegic after two hours. Initial laboratory evaluation revealed severe hypokalemia, with normal thyroid function. We performed electrodiagnostic studies including long exercise test as proposed by McManis et al. Nerve conduction study was normal, but marked decrement in CMAP amplitude (up to 60% decrease after 10 minutes) was noted after prolonged exercise. Despite oral and intravenous potassium replacement, serum potassium level was not corrected as expected. The unusual clinical course prompted for evaluation of secondary etiologies. Abdomen computed tomography scan revealed a 1.5 x 1.0 cm-sized mass in the left adrenal gland. Aldosterone to renin ratio was elevated, suggestive of primary hyperaldosteronism. Genetic study for CACNA1S mutation turned negative. After receiving laparoscopic adrenalectomy, the patient experienced no further attacks, and also was able to stop his antihypertensive medication. LET may show abnormal results in condition with reduced membrane excitability, even without true channelopathy.

THE APPLICABILITY OF CORNEAL CONFOCAL MICROSCOPY IN SMALL FIBER NEUROPATHY

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According to international criteria, the diagnosis small fiber neuropathy (SFN) is based on clinical symptoms in combination with a reduced intraepidermal nerve fiber density (IENFD) in skin biopsy and/or abnormal temperature threshold testing (TTT). The sensitivity of skin biopsy is moderate to good, although IENFD is normal in about 67% of patients with SFN complaints. Furthermore, TTT is a widely available diagnostic tool, but lacks specificity. Corneal confocal microscopy (CCM) has been described and is used in clinical practice as an objective, non-invasive diagnostic tool to detect small nerve fiber damage in patients with diabetes mellitus. This study examines the applicability of CCM in patients with SFN, and the value of CCM as an additional diagnostic tool in SFN. We will include 20 healthy participants to compare the results with the recently published CCM normative values, and 200 patients referred to the SFN center Maastricht with the clinical picture of SFN. Corneal nerve fiber density (CNFD), branch density (CNBD), fiber length (CNFL), and the tortuosity coefficient (CNFT) will be determined in all participants. The results will be compared with the IENFD and TTT. Preliminary results will be presented.

CHALLENGES IN NEUROLOGICAL PRACTICE IN LAO P.D.R

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Located in South East Asia, Lao PDR is a landlocked country with a population of about 6.8 million inhabitants. The health indicators are among the lowest in South East Asia. The total health caregivers in 2014 consisted of 14,964 persons corresponding to a ratio of 2.2 health workers per 1000 inhabitants. The main network for health care service provision remains the public system. Its health care facilities consist of four central teaching and referral hospitals; five regional hospitals, including one teaching hospital; 13 provincial hospitals; 135 district hospitals, and about 970 health centers. Only one in seven sick people receives modern health care treatment. Most people rely on self-medication and/or reliance on self-healing. Neurological care is a very new field. Knowledge of common neurological disorders among both the Lao population and medical staff is only beginning to be spread. There are three neurologists in the country. Six neurology residents are currently being trained in a three-year program supported by the Association pour la Promotion des Neuro-sciences au Laos (Association for the promotion of neuro-sciences in Laos) and the ASEAN Neurological Association. Indeed, resources

are scarce. In the Peripheral Nerve Diseases domain for example, we have only one Electromyography Machine that was only temporary used when EMG experts from France and from Singapore came to teach residents. A significant mismatch between the provision of specialized neurologic services and the needs for them exists, especially in rural areas. Also, health insurance is not available for the majority. As a consequence, patients have to bear the costs themselves, which constitutes a limit to the access of available healthcare facilities. Neurologic training centers, laboratory facilities and equipments are limited. Optimizing available human resources, integrating primary, secondary, and tertiary healthcare tiers and making medical treatment more affordable are need to improve neurologic care in the developing world. In certain low-income countries with limited human and financial resources, it may be difficult for governments to apply some of these recommendations on their own. In these circumstances, it is suggested that countries work with international agencies, nongovernmental organizations or other partners to put their plans into practice.

THROMBOEMBOLIC EVENTS IN INFLAMMATORY NEUROPATHY PATIENTS ON IVIG

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Observational data suggest intravenous immunoglobulin (IVIg) increases risk of thromboembolic events (TEE). Traditional vascular risk factors influence individual risk but the pro-coagulant mechanism of IVIg is not understood. Our aim was to ascertain frequency of and risk factors for TEE, arterial (ATE) and venous thromboembolic events (VTE) in neuromuscular patients receiving regular IVIg. We performed a retrospective case-note review of 112 inflammatory neuropathy patients receiving regular IVIg treatment. We collected the following data over a 30 month study period (January 2014-June 2016): event occurrence and date, neuropathy diagnosis, dose, frequency, vascular risk factors, pre and post-treatment IgG levels and plasma viscosity. The cohort was made up of CIDP (58.9%), MMN (36.6%), sensory neuropathy/ neuronopathy (4.5%). Patients received a mean (S.D) dose of 1.6(1.2) g/kg/month, range:0.2-6.5g/kg/month; at a mean (S.D.) interval of 4.4(3.0) weeks, range:1-18 weeks. Twelve TEEs were documented during the study period; including 6 MIs, 2 CVAs, and individual occurrences of TIA, DVT, PE, SVC obstruction due to central line thrombosis. In the IVIg cohort, TEE incidence (95%C.I.)= 42.1 (18.6, 67.1)/1000 patient-years was higher than population-based estimates from UK hospital coding records over the same time period= 15.29 (15.25, 15.33) /1000 patient-years. IVIg-ATE incidence= 32.1(11.1, 53.1)/1000 patient-years; UK population-ATE incidence= 12.9 (12.8, 13.0)/ 1000 patient-years; IVIg-VTE=10 (1.4, 22.8) /1000 patient-years UK population-VTE incidence= 2.37 (2.36, 2.39)/ 1000 patient-years. In IVIg patients who had an event, age (*p=0005*) and QRISK2 score (*p=0.01*) were higher and dose/ day (*p=0.008*) was lower than those who did not have an event. There was no difference in dose/ kg/ month (*p=0.66*), treatment interval (*p=0.62*), post-treatment plasma viscosity (*p=0.09*), IgG level (*p=0.28*) or ΔIgG (*p=0.08*). This analysis suggests TEE incidence is higher in IVIg treated patients than comparable population-based rates. Examination of TEE occurrence in age and vascular risk factor matched IVIg-treated and IVIg-naïve individuals is required to appreciate the excess risk associated with IVIg treatment.

PREDICTIVE FACTORS OF LONG-TERM DISABILITY IN CIDP

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Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a disabling disease and about 10% of patients may become persistently disabled over time. Our aim was identify clinical prognostic factors of long-term disability in a large series of CIDP patients. We collected data from 50 CIDP patients with definite diagnosis according EFNS/PNS criteria and positive response to first-line therapies (immunoglobulin or corticosteroids) including sex, age of onset, phenotype, disease duration, course of disease (monophasic/relapsing-remitting or chronic progressive) and disability at the time of diagnosis assessed using the modified Rankin Scale (baseline mRS). All patients had clinical assessment of disability through mRS within the last 6 months (last mRS). Ordinal logistic regression model was applied to evaluate the relationship among the clinical parameters and last mRS, considered as ordinal outcome (0-6). Anova test for repeated measures was applied to test the overall effects of different course on disability accumulation while t-test was performed to evaluate inter-group differences for parametric variables. We found a significant relationship between last mRS and the course of disease [p<0.000, z=4.05, OR: 14.91]. Disability accumulation was greater in patients with chronic progressive course than those with monophasic/relapsing-remitting course of disease [p=0.04]. Moreover, patients with progressive course were older [p=0.01]. Our data suggest that chronic progressive course of disease may be a major negative prognostic factor for long-term disability in CIDP patients. To note that a chronic progressive course of disease is also associated with an older age from the beginning and a more pronounced worsening over the course of disease.

MRI BIOMARKERS TO ASSESS PROXIMAL NERVE INJURY IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

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An unresolved problem in the treatment of inflammatory neuropathies is the lack of valid and reliable diagnostic biomarkers to evaluate axonal damage. We investigated if "diffusion tensor imaging" (DTI) and MRI T1w multi echo Dixon imaging are eligible methods to determine proximal nerve injury in chronic inflammatory demyelinating polyneuropathy (CIDP). In this prospective observational cohort study the sciatic nerve of 11 CIDP patients and 11 age matched healthy controls was investigated. All subjects underwent multimodal MRI imaging to determine fractional anisotropy (FA) and muscle fat fraction of the biceps femoris and quadriceps femoris muscle. Patients were evaluated by MRI, clinical examination and nerve conduction studies at baseline and after six months. The mean fractional anisotropy (FA) value was significantly lower in the sciatic nerve from CIDP patients compared to controls. Fat fraction of the biceps femoris and quadriceps femoris muscle were significantly higher in CIDP patients compared to controls.
MRI outcome parameters remained unchanged after six months. Our study demonstrates the utility of MRI imaging to differentiate between "healthy" and functional constricted proximal nerve segments. We postulate that DTI and Dixon MRI might be eligible methods to assess proximal nerve damage in CIDP.

THE FUNCTIONAL IMPACT OF PERIPHERAL MYELIN PROTEIN 2 (PMP2) FOLLOWING DEMYELINATION IN VITRO AND VIVO

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The presence of peripheral myelin protein 2 (PMP2) has been known for decades, but its functional role was uncovered only recently. Recent characterization of PMP2-deficient mice revealed a role of PMP2 in the lipid homeostasis of myelinating Schwann cells. In this study, we analyzed the functional impact of PMP2 on myelination. To decipher the role of PMP2, experimental demyelination was performed in myelinating dorsal root ganglia cultures, and in vivo re-myelination was assessed after experimental peripheral nerve damage. We used the myelinating dorsal root ganglia (DRG) model in PMP2-deficient Schwann cell cultures, combined with an established de- and remyelinating protocol in order to analyze myelination in vitro. We also performed experimental nerve crush in PMP2-deficient mice. Morphometric parameters were defined for the in-vitro experiments and functional parameters such as nerve conduction velocity and the clinical score were additionally measured for the in vivo experiments. Structural analyses of the DRG cultures revealed fibers expressing myelin basic protein (MBP) and PMP2, as well as fibers positive for MBP alone. In contrast to our previous in vivo data, we were also able to detect myelin segments that stained positive for PMP2, but were negative for MBP. PMP2-deficient DRG-cultures demonstrated slightly greater nodal lengths than the control cultures. This trend was significantly augmented after in vitro de- and remyelination, which also resulted in decreased internodal lengths only now, while conserving an intact myelin structure. Concomitantly, in vivo nerve crush gives rise to a more severe phenotype in PMP2-deficient mice than in wild-type controls. Consistent with this, nerve conduction studies showed a delay in remyelination, and analysis of semi-thin sections demonstrated an altered fiber structure in the peripheral nerve biopsies. Together, these data suggest that in addition to its role in glial cell lipid homeostasis, PMP2 also plays a role in remyelination of the injured peripheral nervous system.

LENALIDOMIDE-RESPONSIVE ANTI-MAG NEUROPATHY

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Anti-MAG neuropathy remains a difficult diagnosis to treat given its limited therapeutic options. Of all interventions, Rituximab has emerged as the most effective, although its effect has been with mixed results, especially in patients with advanced axonal loss. Lenalidomide is another promising immune modulating therapy, whose effect has been well demonstrated in neuropathy associated with POEMS (Polyneuropathy, Endocrinopathy, Organomegaly, M-spike protein, and skin changes) syndrome, a condition that has several striking parallels to anti-MAG neuropathy. The use of Lenalidomide has not been previously described in anti-MAG neuropathy. Herein, we describe a case of Lenalidomide-responsive anti-MAG neuropathy in a patient with advanced axonal loss.

PROPOSAL OF DIAGNOSTIC CRITERIA FOR POEMS SYNDROME WITH THE HIGH SENSITIVITY/SPECIFICITY

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Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is a rare cause of demyelinating neuropathy associated with plasma cell dyscrasia and VEGF overproduction. Several diagnostic criteria for the disorder have been published, but sensitivity/specificity analyses, and their validation have never been performed. The aim of this study is to establish valid diagnostic criteria for POEMS syndrome. 104 consecutive POEMS patients, seen at Chiba University Hospital since 2000, were screened. Of these, we have set a gold standard group of POEMS syndrome, based on treatment response and exclusion criteria during 1-year follow-up, and 66 patients was diagnosed as having definite POEMS syndrome. We also collected 30 patients with CIDP (demyelinating neuropathy control) and 30 with multiple myeloma, primary amyloidosis, or MGUS (M-protein control). Criteria for POEMS syndrome was defined as having two of the three major criteria (polyneuropathy, M-protein, and elevated serum VEGF level) and at least two of the four minor criteria (extravascular volume overload, skin changes, sclerotic bone lesions, and thrombocytosis) which were determined by logistic regression analyses. According to the criteria the sensitivity was 99%, and the specificity was 100%. Our results indicate that the proposed criteria have an excellent diagnostic accuracy, and are useful in clinical practice, presumably leading to early diagnosis and treatment.

CHANGES IN PAIN THRESHOLD BY SKIN TEMPERATURE: A STUDY BY INTRAEPIDERMAL ELECTRICAL STIMULATION

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Intraepidermal electrical stimulation (IES) is a new technique to that assesses the function of A-delta fibers in the epidermis. Using this technique, we previously reported that the epidermal pain threshold was two-hold in asymptomatic diabetic patients than in normal subjects (Muscle Nerve 54: 146-149, 2016). Subsequently, we reported that the elevated pain threshold negatively correlated with intraepidermal nerve fiver density (JPNS 18: S112, 2013). Empirically, it is known that lowering the skin temperature makes it less likely to feel pain. Therefore, it is necessary to investigate whether the results of IES are affected by skin temperature. The aim of this study was to investigate the influence of a low skin temperature on pain threshold. We recruited 10 subjects with a mean age of 54.6 years. For nociceptive stimulation, we used an IES method with a concentric micro-needle electrode that was developed specifically for the selective stimulation of cutaneous A-delta fibers. We placed the IES electrode onto the extensor digitorum brevis and began stimulation with intensity strong enough for the subject to feel a pricking sensation, then reduced the current in steps of 0.01mA until no sensation was felt. We defined pain threshold as the minimum electrical intensity at which a subject felt a pricking sensation. Firstly, we measured pain threshold at skin temperature above 35 degrees Celsius. Then, we put an ice pack on the extensor digitorum brevis for 10 min to lower the skin temperature, and measured pain threshold at skin temperatures below 33 degrees. Mean pain threshold values above 35 degrees and below 33 degrees of skin temperature were 0.102 and 0.33 mA (p<0.05), respectively. Our data indicated an elevated pain threshold in epidermis with a low skin temperature. One of most common methods for nociceptive stimulation is painful CO_2 laser stimulation. Some CO_2 laser stimulation studies reported pain threshold increased with a low skin temperature. Our result is similar to that of CO_2 laser stimulation. Pain threshold using IES is very easy and non-invasive technique. It may be useful for the evaluation of small fiber neuropathy.

CHANGES OF SERUM IGG DIMER LEVELS AFTER TREATMENT WITH IVIG IN GUILLAIN-BARRÉ-SYNDROME

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Intravenous immunoglobulins (IVIg) are an effective treatment in Guillain-Barré-Syndrome (GBS). In most patients, the optimal IVIg dose and regime is unknown. In serum and IVIg preparations, immunoglobulin (Ig) G form IgG dimers, which are assumed to consist of idiotypic/anti-idiotypic antibody pairs. However, data about kinetics of IgG dimer formation in GBS are lacking.
To study IgG dimer formation, C57Bl/6 mice were injected with IVIg and anti-GD1b antibody or PBS. Blood sera were collected 24h, 48h and 1 week post injection. A third cohort received an anti-GD1a/GT1b antibody and blood was collected 48h post injection. IgG was extracted and subtyped into polymeric, dimeric and monomeric fractions using the ÄKTA FPLC system. Dialysed dimeric and monomeric IgG fractions were examined for the presence of anti-ganglioside antibodies by anti-ganglioside antibody ELISA. Further, blood samples from 10 GBS patients were collected before (pre-IVIg) and after treatment with IVIg (post IVIg). Serum samples were examined for IgG dimers and monomers using the ÄKTA FPLC system. In the mouse model, a maximum peak of IgG dimer formation was observed 48h post injection. In GBS patients' samples, IgG serum levels and IgG dimer content was significantly higher after treatment with IVIg. We demonstrate here the feasibility to assess IgG dimer formation in an animal model and in GBS patients' samples after treatment with IVIg. 48h after IVIg treatment appears to be the optimal time point to assess IgG dimer formation. Further studies are warranted to determine the utility of IgG dimer formation as surrogate marker for treatment response in GBS.

OPTIMIZING GENE EXPRESSION ANALYSIS IN CMT1A SKIN BIOPSIES.

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Development of outcome measures for clinical trials in CMT1A is a major challenge given the slowly progressive nature of the disease. Outcome measures can be used to measure a) target engagement for a given therapy, as well as b) disease process and c) disease burden. Several candidate therapies have been shown to reduce *Pmp22* levels in CMT1A rodent models and thereby ameliorate the symptoms of *Pmp22* overexpression. Measuring *PMP22* mRNA reduction in human trials has so far been limited to analysis of skin biopsies by qRT-PCR, which did not demonstrate clear elevations of *PMP22* mRNA during, nor a reduction following, ascorbic acid trials. The analysis of skin biopsies is hampered by variable amounts of Schwann cells (SC) in skin biopsies, as well as the variable amount of PMP22 in SC as previously established by immuno-EM in CMT1A skin biopsies (Katona et al., 2009). Therefore, it is important to develop optimal normalization criteria to address the variability inherent in skin biopsy analysis. Ideally this will employ normalization to SC-specific genes that are not altered by CMT1A status. To optimize normalization, we have performed RNA-seq analysis of skin biopsies from patient and control skin biopsy samples. Analysis of these data after normalization to read depth indicated that *PMP22* levels were 1.5 fold higher in CMT1A patient samples compared to control skin biopsies. However, there was significant variability in *PMP22* levels particularly in CMT1A samples, which may be due to variable amounts of Schwann cells in CMT1A skin. Using a combination of SC-specific genes for normalization, we were able to reduce the apparent variability and optimize the differential levels between CMT1A and control skin biopsy samples. We also identified other SC-specific genes that were apparently induced in CMT1A skin biopsies relative to control. These studies provide a new framework for gene expression analysis in skin biopsies, enabling more precise evaluation of *PMP22* levels in clinical trials for CMT1A as a measure of target engagement. In addition, the normalization framework may also be applicable to other types of CMT.

OCTAGAM® FOR NEUROLOGICAL DISORDERS: FOCUS ON CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY – DATA FROM 3 OBSERVATIONAL STUDIES

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common chronic autoimmune neuropathy, with an estimated prevalence of between 1 and 9 per 100,000 people. It can cause temporary disability in the affected individuals and may eventually lead to permanent disability or death. CIDP is commonly treated with intravenous immunoglobulin (IVIG) therapy or corticosteroids. Octagam® 5% is licensed for CIDP in France, while Octagam® 10% is licensed for CIDP in Germany and Belgium. This analysis presents data from three open, multicenter, non-interventional, single-arm, non-controlled studies of a Post-Authorisation Safety Surveillance (PASS) program for the subset of patients receiving octagam® 5% or 10% for neurological indications, focusing on patients with CIDP. Briefly, data from in- and out-patients in Austria, France, Germany, and UK treated with octagam® for neurological disorders were collected by physicians and analyzed to assess safety and tolerability of the treatment. Of 2314 patients included in the three studies, 260 patients (11.2%) received octagam® for neurological indications, of which 58 patients (22.3%; mean age 64.6 years [range 18–88]) had CIDP. The mean dose of octagam® per course was 0.8 g/kg BW for patients with CIDP; for the other neurologic indications, the dose ranged from 0.2 (for multiple sclerosis) to 1.4 g/kg BW (for Guillain-Barré syndrome). Premedication was not needed in 84.3% of these patients. The development of clinical appearance since last observation (mean: every 9.7 months) was assessed for 41 of the 58 CIDP patients by their treating physicians. The majority of observations (81.1%) assessed the patients as stable and 16.6% showed even an improved clinical appearance. Only 2.3% of the observation periods resulted in deteriorations. Adverse drug reactions were rare: Of the 3374 infusions received by patients with neurological disorders, 0.44% of infusions were associated with an ADR (0.61% of infusions in CIDP patients). Overall, treatment with octagam® was effective and well-tolerated in patients with CIDP. These results are consistent with data for the overall patient population (including patients with primary and secondary immunodeficiencies, dermatological and other diseases).

LYSOPHOSPHATIDIC ACID CONTRIBUTES TO A SCHWANN CELL PHENOTYPE ASSOCIATED WITH PERIPHERAL NERVE INJURY

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Lysophosphatidic acid (LPA) is a pleiotropic signaling lipid that acts as ligand for at least six specific G protein coupled receptors. Schwann cells (SC) are known to mainly express the LPA_1 receptor subtype. An emerging body of in vivo evidence has linked LPA with injury induced peripheral nerve demyelination as well as neuropathic pain. However, the molecular mechanism underlying its demyelinating effect has remained largely unclear.
Myelinated dorsal root ganglia (DRG) cultures were treated either with LPA, LPA + AM095 (LPA_1 antagonist) or vehicle. We assessed myelin basic

protein, tumor necrosis factor alpha (TNF-alpha) as well as the SC differentiation marker Sox10 by immunocytochemistry. Additionally, myelin was investigated by Sudan black staining. To better understand the relevance of LPA_1 signaling for demyelination in vivo, we performed sciatic nerve crush in C57BL/6 mice treated with AM095 at 10 mg/kg in order to study Schwann cell expression of TNF-alpha, Sox10 and Sox2, a marker for SC dedifferentiation, by immunohistochemistry.
In DRG cultures, LPA caused a significant reduction of myelin as demonstrated by both Sudan black staining and immunocytochemical analysis of myelin basic protein. Demyelination was paralleled by an upregulation of TNF-alpha as well as downregulation of Sox10. LPA mediated effects were found to be blocked by addition of the LPA_1 receptor antagonist AM095. In C57BL/6 mice, AM095 treatment prior to crush injury increased Sox10 expression in SCs in the distal nerve stump while reducing the number of cells expressing Sox2. These data indicate that LPA may be a critical factor to shift SCs towards an injury-associated phenotype and contribute to the onset of Wallerian degeneration.

IN VITRO EFFECTS OF PURE GLYPHOSATE VS. GLYPHOSATE-BASED HERBICIDE ON PERIPHERAL NERVOUS SYSTEM MYELINATION

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Glyphosate-based formulations comprise the world's most commonly used herbicides. In non-resistant plants, glyphosate exerts toxic effects most likely via inhibition of aromatic amino acid synthesis by interfering with the shikimate pathway. While glyphosate is the active ingredient, herbicidal formulations contain several adjuvants, including polyethoxlated alkylamines (POEAs). Although glyphosate has long been considered safe for use in humans and animals, several studies have implicated glyphosate and/or the commonly used adjuvants in cytotoxicity, carcinogenicity and endocrine disruption. Furthermore, glyphosate-based herbicide has been reported to mediate neurotoxicity in immature rat hippocampus involving glutamate excitotoxicity. However, it remains unclear whether glyphosate alone or in combination with its adjuvants may have detrimental effects on myelin integrity in the peripheral nervous system.
Myelinated dorsal root ganglia (DRG) cultures were treated over the course of ten days with either pure glyphosate or a glyphosate-based herbicide at concentrations of 0.05 %, 0.005 % and 0.0005 %. The concentration of the glyphosate-based herbicide was matched with regard to glyphosate content (36 %). Controls were treated with equal amounts of vehicle adjusted for the pH. Subsequently, cultures were stained with sudan black and myelin content was assessed by determining the number of internodes per neurons.
While glyphosate, regardless of its concentration, did not show any effect on myelin content, the glyphosate-based herbicide caused significant demyelination in a concentration- dependent manner. Notably, at 0.05 %, DRG cultures were completely devoid of myelin and appeared severely necrotic.
These data raise the possibility that not glyphosate itself, but rather the adjuvants in glyphosate-based herbicide formulations may cause demyelination. The open question whether demyelination is a direct effect of the adjuvants or a consequence of increased cellular glyphosate uptake due to permeabilization warrants further investigation.

QUANTITATIVE AUTONOMIC ASSESSMENT IN GUILLAIN-BARRÉ SYNDROME

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In Guillain-Barré syndrome (GBS), autonomic dysfunction is common and accounts for significant morbidity and mortality. There have been many studies investigating the electrodiagnosis of GBS but few have studied autonomic dysfunction in GBS. The current study comprehensively investigates quantitative autonomic function in patients with GBS and its variant. Ten GBS patients were prospectively recruited and the results were compared to 10 age- and gender-matched healthy controls. A series of autonomic function tests including computational (power spectrum analysis of heart rate variability (HRV) and baroreflex sensitivity (BRS) at rest) and challenge tests (deep breathing, eyeball compression, active standing, Valsalva manoeuvre, isometric exercise and ice-water hand immersion) were performed. Parasympathetic function was represented by high frequency (HF) HRV, heart rate responses to deep breathing, eyeball compression, Valsalva manoeuvre and active standing. Sympathetic function was represented by low frequency (LF) HRV, blood pressure responses to active standing, sustained handgrip and ice-water hand immersion. In the frequency domain analysis of HRV, low frequency (LF: 89.47±85.92 vs 226.97±158.16; p=0.027), high frequency (HF: 35.10±37.18 vs 158.11±140.97; p=0.008) and total power spectral densities (PSD: 188.03±121.59 vs 532.71±359.57; p=0.015) were significantly reduced in patients compared to controls. The mean up slope (7.38±4.41 vs 11.86±5.53; p=0.034), down slope (7.32±4.53 vs 13.41±5.07; p=0.011) and total BRS slope (7.32±4.37 vs 12.65±5.24; p=0.024) were significantly lower in the GBS group. The diastolic rise in blood pressure upon ice-water hand immersion was significantly lower in GBS group compared to controls (3.1±4.0 vs 14.0±11.3; p=0.008). Our findings suggest that computation dependent tests (HRV and BRS) were sensitive at detecting autonomic dysfunction and baroreceptor reflex insensitivity in GBS patients. In contrast, ice-water hand immersion was the only reliable challenge test making it useful as a bedside measure of autonomic function in GBS patients.

DIFFERENT AXONAL DYSFUNCTION PATTERN IN SEROPOSITIVE AND SERONEGATIVE SJÖGREN'S SYNDROME

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Sjögren's syndrome (SS) is an autoimmune disease that affects both East and West. Nevertheless, we still have limited knowledge of how autoantibodies in SS affects the peripheral nervous system. In this study, we investigated the peripheral neuropathy in SS and sicca complex using the nerve excitability test, to elucidate how peripheral nerves are affected. We have enrolled a total of 22 patients with SS or sicca complex. Of these, two patients were excluded due to co-morbid carpal tunnel syndrome. Each patient received clinical evaluation, examination for SSA/SSB antibodies titer, the nerve excitability test, conventional thermal quantitative sensory test, and conventional nerve conduction study. Compared to 33 normal control subjects, motor nerve excitability test of SS patients with positive SSA or SSB antibodies (n = 14) were found to have increased rheobase (P<0.05), increased relative refractory period (RRP) (P<0.01), increased refractoriness at 2.5 ms (P<0.01), increased accommodation toward depolarizing current in threshold electrotonus (TE) (P<0.05), and decreased superexcitability (P< 0.05). The sensory axonal study in seropositive SS also revealed increased RRP (P<0.01), increased refractoriness at 2.5 ms (P<0.01), and increased accommodation toward hyperpolarizing current in threshold electrotonus (TE) (P<0.05). Meanwhile, in seronegative SS and sicca complex (n = 6), we found no significant axonal properties changes. The present study revealed that peripheral nerves are affected differently in seropositive SS and in seronegative SS/sicca complex. In seropositive SS, motor axons tended to be depolarized, and both sensory and motor axons have increased refractoriness. The findings suggested that SSA and SSB antibodies might play a role in the inactivation of transient sodium channels. The effects of the antibodies on transient sodium channels might be the basis of peripheral neuropathies and even cardiac arrhythmias and heart block in SS.

GENOME-WIDE ASSOCIATION STUDY IDENTIFIES POTENTIAL GENETIC MODIFIERS IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A

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Charcot-Marie-Tooth disease type 1A (CMT1A), caused by the *PMP22* duplication on chromosome 17p11.2, is the most common subtype of inherited peripheral neuropathies and affects 1 in 10,000 individuals worldwide. While sharing the same genetic cause, CMT1A patients often present great variability in their phenotypic presentation and disease severity. The cause of the phenotypic variability is largely unclear. In this study, we performed genome-wide association study (GWAS) to identify novel genetic modifiers of various phenotypes in CMT1A. DNA samples from 971 CMT1A patients were genotyped on Illumina OmniExpress platform. After standard quality control, the dataset includes 600k markers in 857 individuals (644 individuals from European ancestry, and 213 individuals from Asian ancestry). We focused our analyses on the European population. Logistic regression in PLINK was used to analyze the association between the clinical outcomes and patients' genotypes in an additive model. For CMT neuropathy score (CMTNS), the analysis was performed using linear regression in PLINK, adjusting for patients' age. The analyses yielded several suggestive association signals. An association peak on chromosome 6 was identified in difficulty with eating utensils (lead SNP rs12192704, chr6:30792270, P=1.15E-06, odds ratio=3.25). The peak is located within a non-coding gene *LINC00243*. Hearing loss showed an association peak on chromosome 5 (lead SNP rs7720606, chr5:126551732, P=2.22E-07, odds ratio=3.457), located in an intergenic region near the *MEGF10* gene. In foot plantar flexion, an association signal was identified in the *DSCAM* gene on chromosome 21 (lead SNP rs2249498, chr21:41431874, P=5.13E-07, odds ratio=2.437). CMTNS showed an association signal on chromosome 1 (lead SNP rs12137595, chr1: 4094068, P=1.14E-07, beta=3.014), located within an intergenic region close to *DFFB*, *C1orf174*, and *LINC01134*. While these suggestive signals require further validation, our study provides novel insights into the genetic architecture of CMT1A. Novel genetic modifiers may

serve as potential targets for therapeutic interventions in the future.

MYASTHENIA GRAVIS? MYOPATHY? OR A NEUROPATHY?

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We present an intriguing diagnostic puzzle, that was eventually cracked serendipitously. A 50-year-old man was seen for bilateral ptosis. Evaluation for myasthenia gravis was negative. Nevertheless, a diagnosis of ocular myasthenia gravis was made and he was put on pyridostigmine. He did not respond. The ptosis progressively worsened. He sought a second opinion. At this evaluation, he was noted to have complex ophthalmoplegia without diplopia, bilateral facial weakness and mild bulbar weakness. He had no sensory complaints. The limb examination was remarkable for slightly reduced reflexes, normal strength, and other than increased vibration threshold at the toes, intact sensory examination. Repeat serological and electrodiagnostic work-up for myasthenia gravis was negative. A myopathic disorder such as chronic progressive external ophthalmoplegia was considered. Serum creatine kinase and lactate were normal. He underwent biceps muscle biopsy which showed increased COX-negative and SDH positive fibers, supporting the then clinical impression of a mitochondrial cytopathy. At this point, he underwent blepharoplasty to improve his vision. Routine histological examination of the levator palpebrae muscle showed amyloid deposits. This prompted a review of the earlier biceps biopsy, which revealed amyloid deposits that were not appreciated before. At this point, the significance of the patient and his son's history of lattice corneal dystrophy became apparent. He also reported that his late mother had similar facial appearance as his. The patient's nerve conduction study showed length-dependent sensory axonal polyneuropathy, right carpal tunnel syndrome and bilateral facial neuropathy. He had no definite symptoms of autonomic neuropathy. Cardiac evaluation was unremarkable. The final diagnosis of familial gelsolin amyloid polyneuropathy was made. Genetic confirmation for the patient and his family is being planned. We highlight the key clinical features of gelsolin neuropathy. The symmetric cranial neuropathy can resemble a muscle or neuromuscular junction disorder and the relative sparing of the cardiac muscle, somatic and autonomic nerves contrasts with transthyretin-related amyloid polyneuropathy.

IMPLICATIPON OF RARE Nav1.7 VARIANTS IN PAINFUL DIABETIC NEUROPATHY

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Neuropathy is one of the most common long-term complications of diabetes. Furthermore, 25% to 50% of diabetic neuropathy patients will develop neuropathic pain. The pathophysiology of neuropathic pain in diabetic peripheral neuropathy is complex and not fully understood. A potential mechanism is a change in voltage gated sodium channels, such as Nav1.7. Loss of function mutations in this channel cause insensitivity to pain, whereas gain of function mutations have been linked with different pain syndromes including small fiber neuropathy. In a cohort of 190 patients with diabetic peripheral neuropathy we investigated whether mutations in Nav1.7 were associated with diabetic neuropathic pain. Twelve Nav1.7 variants were identified in nine participants all within a cohort of 111 participants with painful diabetic peripheral neuropathy. Five of these variants were previously associated with pain disorders: V991L, M932L; W1538R, R185H, L1267V. Among the other variants two of them met the criteria of potential pathogenicity based on predictive algorithms and were further studied. Functional analysis by whole cell patch clamp showed that one of these variants (M1852T) drastically impairs the inactivation of the channel by shifting the steady-state fast-inactivation towards more depolarizing potentials. There were no phenotypic difference between those participants with pathogenic variants and those participants without pathogenic variants. No rare Nav1.7 variants were found in 79 participants with painless diabetic peripheral neuropathy. These observations suggest that mutations in Nav1.7 may contribute to painful diabetic peripheral neuropathy.

ANTI-FGFR3 ANTIBODIES AND SENSORY-NEUROPATHY. A FRENCH PROSPECTIVE STUDY

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Dysimmune sensory neuronopathies (SNN) encompass paraneoplastic SNN and SNN associated with systemic autoimmune diseases such as Sjögren syndrome, lupus or inflammatory bowel or rheumatic diseases but also a number of apparently idiopathic cases. Biomarker antibodies are well-known in paraneoplastic SNN but are lacking in non

paraneoplastic cases. From a mono-center retrospective study we identified in 2015 anti-FGFR3 antibody as a potential biomarker of dysimmunity in patients with idiopathic or systemic autoimmune disease associated sensory neuropathy. The identified patients were more frequently women and had a non lenthg dependent neuropathy suggestive of SNN. Anti-FGFR3 antibody was the only immunological marker in 2/3 of cases at initial work-up although 1/3 of patients eventually developed with time systemic autoimmune disease. To confirm the incidence and the clinical pattern of patients with anti-FGFR3 antibodies we launched a prospective multicenter French study including patients with a sensory neuropathy suspected to be a SNN of no paraneoplastic, genetic or metabolic origin. We present here the results on the first 82 included patients compared to 54 healthy blood donors. Anti-FGCR3 antibodies were searched by Elisa using the TRK intracellular domain of the protein (Invitrogen©). We found 7 patients positive for anti-FGFR3 antibody (8.5%). These patients were 5 women and 2 men aged 63.7 years as a mean (44-91). The neuropathy was acute and subacute in one patient respectively and progressive in the 5 others. Six patients fulfilled the diagnosis criteria of SNN and the last one had a sensory neuropathy in the lower limb with abnormal sensory action potentials in the four limbs suggesting SNN without reaching the requested criteria. One patient developed uveitis which is a new symptom with anti-FGFR3 AB. An unclassified dysimmune context was present at the initial work up in 3 patients and one patient developed Sjögren syndrome with follow-up. As a whole the clinical pattern of these patients is consistent with that of the initially published series. The lower prevalence of positive sera may be due to more stringent criteria used for Elisa but needs to be confirmed on the complete prospective series.

PERIPHERAL NEUROPATHY RESEARCH REGISTRY (PNRR)

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The Peripheral Neuropathy Research Registry (PNRR) is a multicenter collaborative research project sponsored by ***the Foundation for Peripheral Neuropathy*** to advance the science in distal symmetrical polyneuropathies (DSP). The registry was designed to prospectively characterize clinical phenotype and natural history of patients with DSP and obtain biofluids to identify new causes and genetic modifiers of DSP with careful genotype/phenotype correlations, and to develop biomarkers. The enrollment in the registry is still ongoing but an interim analysis was carried at the end of December 2016. Eligible study participants were 18 years or older with a diagnosis of idiopathic, diabetic, chemotherapy- or HIV-induced peripheral neuropathy. They were examined by a physician at one of the six consortium members (Johns Hopkins University School of Medicine, Icahn School of Medicine at Mount Sinai Medical Center, Beth Israel Deaconess Medical Center, Northwestern University Medical Center, University of Utah Medical Center and Kansas University Medical Center). The collected data set included (1) a detailed questionnaire, discussing their symptoms, medical history and family history, (2) a standardized neurological examination form, (3) electrodiagnostic evaluation and (4) diagnostic laboratory testing. Blood samples (whole blood, plasma and serum) were collected for future biomarker and genotyping evaluations. At the end of 2016, complete data sets and blood samples were collected from 1150 patients. 31% had diabetic PN, 10% had HIV-associated PN, 7% had chemotherapy induced PN and 52% were diagnosed with idiopathic PN. Detailed analysis of clinical presentation, examination findings and diagnostic investigations will be discussed at the presentation. Standardized phenotyping with linked bio-specimen banking will help establish the minimum data set required for neuropathy diagnosis and support genotype-phenotype correlations with next generation sequencing technologies and development of novel biomarkers. PNRR data will improve our understanding of disease mechanisms paving the way for new therapeutic discoveries in painful and non-painful neuropathies.

NEUROPHYSIOLOGICAL MEASURES CORRELATE WITH PATIENT REPORTED SYMPTOMS OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

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Chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of treatment, typically presenting as a sensory neuropathy. Symptoms include pain, paraesthesia, and numbness in the extremities, resulting in functional impairment. Increasingly, patient reported outcomes (PROs) are utilized to accurately examine the impact of CIPN symptoms on patient function. However, the links between objective neurological assessment and PRO measures remain ill defined. This study aimed to identify links between neurophysiological measures and PROs in patients treated with

neurotoxic chemotherapy. Assessments were conducted in 45 patients (F= 31, mean age 53.8 ±1.9 years) who had completed neurotoxic chemotherapy on average 9.7 ± 2 months previously (Platinum-based N=17, Taxane-based N=21 or taxane/platinum combination therapy N=7). Patients reported the presence and severity of neuropathic symptoms via the FACT-Gog Ntx13, a validated patient questionnaire. Clinical neurological assessment was scored using the Total Neuropathy Score clinical version (TNSc), comprising pinprick and vibration sensibility, deep tendon reflexes, strength and patient symptom report. Compound sensory action potential (CSAP) amplitudes were recorded antidromically at the lateral malleolus, stimulating the sural nerve at the mid-calf. Of the total sample, 75% reported lower limb neuropathy, with 44% of patients reporting 'quite a bit' or 'very much' severity of tingling and numbness in their feet. The average sural CSAP amplitude was 10.4±1.1μV and 40% of patients had sural amplitudes below the lower limit of normal for age. The total TNSc score correlated with the PRO FACT-Gog Ntx13 score (r = -.532, P<.001) and sural amplitude (r = -.338, P <.05). Vibration sensibility correlated with the overall FACT-Gog Ntx13 score (r =-.338, P <.05), and sural amplitude (r =-.299, P <.05). Sural amplitude correlated with patient reported severity of numbness and tingling in the lower limbs (r =-.3, P <.05) but not with the overall FACT-Gog Ntx13 score. Patient reports of neuropathic symptoms in the lower limb correlate with both objective neurophysiological and clinical measures of neuropathy severity. Identifying links between objective neurophysiological markers and patient reported outcomes are critical to assess the impact of clinical interventions.

IDENTIFICATION OF FIVE NOVEL MUTATIONS IN BRAZILIAN FAMILIES WITH X-LINKED CMT

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Mutations in the gab junction beta 1-protein gene (*GJB1*) are the second most frequent cause of Charcot-Marie-Tooth disease (CMT), accounting for approximately 10% of CMT cases worldwide. The *GJB1* codes for connexin 32 protein (Cx32). In the peripheral nervous system, the Cx32 is expressed in the Schwann cells and allows intercellular traffic of ions and small molecules between opposed cells. We analysed retrospectively detailed clinical and neurophysiological data of five families carrying novel *GJB1* mutation submitted for testing at our Neurogenetics laboratory. Mutations were identified by bidirectional Sanger sequence analysis of *GJB1* coding region. We identified a total of 11 subjects from five different kindreds with novel mutations (p.A96V, p.L144W, p.L165Q, p.F193S, p.R224L). These five novel mutations segregate with phenotype, are located in highly conserved amino acids among *GJB1* and other gab junction protein sequences and among different species, are not present in any public database (ExAC, dbSNP and 1000 Genome database), and were not found in 100 normal Brazilian controls. *In silico* analysis, predict these variants to be pathogenic, There was no male-to-male transmission; males were more severely affected than females. Four out seven female have subclinical neuropathy and were only identified after clinical and electrophysiological evaluation. The conduction velocities were in the intermediated range in the males patients and higher in the females included in this study. We describe five new pathogenic mutations causing CMTX1 in a Brazilian population and expand the number of causative mutations in the GJB1 gene.

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PURE NEURAL LEPROSY MIMIKING BRACHIAL AND LUMBOSACRAL PLEXOPATHY

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Pure neural leprosy (PNL) is a slowly progressive, predominantly sensory patchy neuropathy presenting with positive and/or negative sensory symptoms, which are usually followed over time by distal asymmetrical weakness. Despite rare, monomelic involvement in leprosy has already been reported. We sought to describe the clinical and electrophysiological patterns of an unusual leprosy neuropathy presentation. Clinical data were retrospectively collected from nine patients who had monomelic involvement and were referred for further investigation to the EMG lab. Seven out nine patients were male. Four patients had a brachial plexus like presentation and five have a lumbosacral plexus like presentation. The initial complaint was hypoesthesia in four patients, tingling in two patients and hypoesthesia with tingling in two patients. Severe pain was observed in just one patient. All individuals from the group of patients with lumbosacral plexus-like presentation and three with brachial plexus-like presentation had no sensory nerve action potentials (SNAPs) for all nerves tested in the affected limb with or without motor involvement. One patient with brachial plexus-like presentation had focal slowing of conduction velocity with temporal dispersion of both median and ulnar nerves in the affected limb. One patient with plexus-like presentation had SNAPs with

low amplitude of all nerves in the affect limb. The diagnosis of leprosy was confirmed by nerve biopsy findings, anti-PGL1 antibody, and positive response to specific treatment. Nerve biopsy was performed in four patients, and the bacillus was found in two. The anti-PGL1 antibody was positive in four patients. Plexus MRI was performed in two patients and was normal. We found the distribution of motor and sensory symptoms were restricted to on limb in this group of patients. As a typically patchy disorder PNL may affect any nerve, although the reason why damage are restrict to only one limb has to be elucidated. The description of these cases increases the clinical spectrum of leprosy neuropathy. This possibility should be considered in the differential diagnosis of patients with plexopathy from endemic areas after excluding other causes.

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A PATIENT WITH ATAXIA WITH OCULOMOTOR APRAXIA TYPE 1 AND SLOW CONDUCTION VELOCITIES

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Ataxia with oculomotor apraxia type 1 (AOA1) is a very complex disorder characterized by an early-onset progressive cerebellar ataxia with cerebellar atrophy and peripheral neuropathy and it is caused by recessive mutations in the aprataxin gene (APTX). When the neuropathy is present, it has been described in 100% of cases as primarily axonal. We describe a case of AOA1 due compound heterozygous mutations in *APTX* associated with demyelinating neuropathy. The patient was born from healthy and non-consanguineous parents and presented in the first decade with progressive cerebellar ataxia, multidirectional ophtalmoparesia, oculomotor apraxia, choreiform movements of limbs and peripheral neuropathy. He had normal cognition and stopped walking at age of 19. Blood tests were unremarkable with normal levels of leucocytes, serum proteins, immunoglobulin, cholesterol, vitamin E, and alfa-feto protein. Brain MRI showed severe cerebellar atrophy. The motor conduction velocity in the upper limbs was slow with preserved amplitudes. The distal latencies and the minimal F wave latencies were prolonged. There was no evidence for superimposed acquired demyelinating neuropathy. Direct sequencing of the APTX gene revealed two variants, c.544-2A>G, p? and c.837G>A; p.W279X. The first variant is novel and affects a highly conserved acceptor splice site of exon 5. The other variant is the most common Portuguese variant, the nonsense mutation W279X is located in exon 6. Parental DNA was tested and confirmed the variants were in different alleles. The presence of a demyelinating neuropathy in AOA1 suggests that phenotypic variability in this condition may be larger than previously considered. At the same time, it increases the differential diagnosis of inherited conditions with cerebellar ataxia and demyelinating neuropathy. Finally, this finding opens the functional effects of the APTX gene.

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SUBCUTANEOUS IMMUNOGLOBULIN IN CIDP: A TWO-YEAR EXPERIENCE

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We report our 2-year experience of subcutaneous immunoglobulin (SCIG) in a cohort of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) from a tertiary care neuromuscular center.

We analyzed data from 13 CIDP patients (8 males and 5 females, mean age: 58 + 11.4 years; mean age at onset: 45.9 + 12.4 years; disease duration: 11.9 + 8.3 years) treated with SCIG and with a follow-up period of 24 months. All patients were previously responders to intravenous immunoglobulin (IVIG). Eight patients had a typical CIDP and five patients had an atypical variant of CIDP.

Five patients switched to weekly maintenance SCIG therapy (continuous regimen) because of short-lasting response to IVIG therapy.

Eight patients with a longer lasting response to IVIG received SCIG with a pulsed regimen similar to that used for IVIG (from 1 to 3 cycles per year); seven of them because of difficulty in hospitalization and one for allergic reaction to IVIG.

Changes in clinical status were assessed over the period of follow-up by using clinical evaluation of muscle strength, modified Rankin scale, overall neuropathy scale and Inflammatory Neuropathy Cause and Treatmentsum score. In 9 patients we evaluated also six minute walking test, 9 hole-peg-test and 10 meter walking test.

All the five patients treated with a continuous regimen of SCIG remained clinically stable throughout the follow-up period. Among the patients receiving pulsed SCIG treatment, 4 out of 8 (50%) responded to SCIG similarly to IVIG, while three patients (37.5%) worsened and needed to be treated again with IVIG and the other one (12.5%) stopped any therapy. Subcutaneously administered immunoglobulin were well tolerated and no patients complained of adverse events.

In conclusion, our findings confirm that continuous SCIG therapy is efficacious in maintaining clinical stability in patients with short-lasting response to IVIG.

Moreover, our data suggest that pulsed therapy with SCIG may represent an alternative therapeutic option for the treatment of a subset of CIDP patients.

ROLE OF X-BOX BINDING PROTEIN 1 (XBP1) IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1B

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Mpz glycoprotein is an abundant product of terminal differentiation in myelinating Schwann cells. The mutant MpzS63del causes Charcot-Marie-Tooth (CMT) 1B disease in humans and a similar demyelinating neuropathy in transgenic mice. MpzS63del protein is retained in the endoplasmic reticulum (ER) of Schwann cells and induces an unfolded protein response (UPR) characterized by activation of PERK, ATF6 and IRE1/XBP1 pathways. We have previously reported that activation of CHOP and GADD34, two downstream mediators of PERK, is pathogenetic in MpzS63del mice (Pennuto, 2008; D'Antonio, 2013) but the role of the other UPR branches remains to be investigated. In this study, we investigated the role of the ER stress sensor enzyme IRE1 and of XBP1 - a transcription factor specifically activated by IRE1 - in MpzS63del pathogenesis. We generated a new mouse model with Schwann cells-specific ablation of XBP1 and in parallel we exploited MpzS63del dorsal root ganglia (DRG) explant cultures in which XBP1 signaling is modulated by gain/loss of function approaches. We observed that absence of XBP1 dramatically worsens hypomyelination and electrophysiological/locomotor parameters in young and adult MpzS63del neuropathic animals. Interestingly we observed that PERK, ATF6 and IRE1-mediated RIDD signalings are upregulated in neuropathic animals lacking XBP1. This suggests that activation of XBP1 targets have an essential role in limiting MpzS63del toxicity, which cannot be compensated by other stress responses. Moreover, we demonstrated in MpzS63del DRG cultures that inhibition of XBP1 splicing by 4u8c (Cross, 2010) decreases myelination whereas activation of XBP1 splicing by quercetin (Wiseman, 2010) slightly ameliorates myelination. Altogether, these data demonstrate that XBP1 pathway has a critical adaptive role in MpzS63del neuropathy and suggest that activation of this pathway may be beneficial for CMT1B and perhaps for a broad range of neuropathies characterized by UPR activation.

CMT1A PATIENTS GET OLD WORSE THAN HEALTHY PEOPLE

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In CMT1A patients, the clinical impairment progressively increases over time and correlates with the axonal loss. Evidence has suggested that the decline of physical performance in CMT1A patients may reflect a process of normal ageing.
The aim of our study was to describe, by a case-control cross-sectional design, the progression of physical impairment with ageing in CMT1A patients.
We enrolled 70 CMT1A patients (26 M; range 20-81 years) and 70 sex- and age-matched healthy controls. To assess physical performance, all patients and controls underwent 10-Meter Walk Test (10MWT), 6-Minute Walk Test (6MWT) and 9-Hole Peg Test (9HPT) of their dominant (d) and non-dominant (nd) sides.
Moreover, to assess clinical disability, impairment and quality of life in the CMT1A group we used the Charcot-Marie-Tooth Neuropathy Score (CMTNS), the MRC Sum Score and the Short Form-36 (SF-36) questionnaire.
The linear regression model was used to evaluate the changes over time of clinical measures in patients and controls. The Chow test was used to determine whether the ageing had a different impact on clinical measures for the two groups.
Physical performance worsened with ageing in both patients and controls, but with a greater slope for CMT1A patients [difference in slopes: 10MWT, 0.15 (C.I. 0.07 to 0.23), $p<0.001$; 6MWT, -4.59 (C.I. -6.41 to -2.77), $p<0.001$; 9HPT-d, 0.59 (C.I. 0.39 to 0.78), $p<0.001$; 9HPT-nd, 0.37 (C.I. 0.20 to 0.53), $p<0.001$].
The rate of deterioration of physical performance was not different between patients and controls until the 50^{th} year of age. After the 50^{th} year of age the rate of deterioration became greater in CMT1A group [difference in slopes: 10MWT, 0.31 (C.I. 0.02 to 0.61), $p<0.039$; 6MWT, -7.13 (C.I. -12.02 to -2.24), $p<0.006$; 9HPT-d, 1.47 (C.I. 0.72 to 2.21), $p<0.001$; 9HPT-nd, 1.11 (C.I. 0.62 to 1.6), $p<0.001$].
Moreover, in CMT1A patients also CMTNS, MRC sum score and SF-36 worsened with ageing and with a greater rate of deterioration after the 50^{th} year of age.
Our study demonstrates that clinical decline in CMT1A patients goes parallel to the normal ageing process until the 50^{th} year of age, whereupon the clinical deterioration accelerates.

IMMUNE CHECKPOINT INHIBITOR-INDUCED ACUTE NEUROPATHIES

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New therapeutic options in immuno-oncology have allowed significant progress in the management of melanomas. Treatment usually consists of a combination of two monoclonal antibodies targeting cytotoxic lymphocyte-associated protein 4 and programmed cell death-1. As a result, the immunologic barrier protecting tumor cells is overcome allowing an antitumor response. We report 6 cancer patients with immune checkpoint inhibitor-induced neuropathies as a complication of this immunomodulating oncologic treatment. Case reports: Our index patient developed severe myalgia 4 days after introduction of ipilimumab-nivolumab followed by painful paresthesias of the face and extremities 1 day after the 2nd cycle of treatment. Generalized areflexic quadriparesis (MRC4) with Gowers'sign and distal loss of vibratory sensation were found. A 5-day course of IVIG plus corticosteroids (CS) had no effect. Three monthly IVIG courses were necessary to improve the deficits at 3 months. A survey of SFNP members revealed 5 other patients with similar acute courses but with phenotypes varying from sensorimotor deficits with areflexia and myalgia to purely sensory ataxic forms following immunomodulating treatment. Work-up including anti-nodal antibodies were negative in 3 patients. From the other 3, 2 had abnormal CSF and 1 had necrotizing myopathy. Detailed repeat NCS demonstrated signs of nerve hyperexcitability and of demyelination or conduction blocks. Evolution was slowly favorable following IVIG and CS. Discussion: Our report underscores that atypical acute generalized demyelinating neuropathies are induced by these novel treatments. They may be associated with severe myalgia or other systemic toxic effects. Discontinuation of the oncologic treatment depends on severity of symptoms. Outcome was slowly favorable following IVIG or CS, albeit slower than in the case of primary inflammatory neuropathies, probably given the long half-life of the monoclonal antibodies.

THE FUNCTIONAL ROLE OF CONNEXINS IN PERIPHERAL MYELINATED FIBERS

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Gap junctions (GJs) are membrane channels found in most tissues connecting adjacent cells or different cell compartments as in Schwann cells. They are involved in electrical connectivity and metabolic homeostasis allowing the passage of small molecules such as ions, second messengers, nucleotides and peptides. An important functional role of peripheral nerve connexins is suggested by their involvement in X-linked inherited neuropathy as well as in acquired neuropathy caused by oxaliplatin. Although GJs play a role in electrical connectivity their specific role in the formation of the sciatic nerve compound action potential (CAP) remains unclear. The aim of this study was to investigate the role of peripheral nerve connexins in the electrical responses of the mouse sciatic nerve under normal and stress conditions. For this purpose we used sciatic nerves of three different mouse models, the Cx32 knockout (KO), Cx29 KO and the Cx32/Cx29 double knockout (dKO) mice. Using our *ex vivo* model for extracellular recordings we exposed sciatic nerves from different genotypes to three different GJ blockers: octanol, 18-beta-glycyrrhetinic acid (GRA) and octanoic acid (OA) and recorded the CAP. Amplitude and duration of the CAP were used as an indication for the effects of the different blockers on the CAP formation. All GJ blockers caused a gradual decrease of the CAP without any changes in the duration of the CAP in all genotypes, suggesting progressive disturbance of axonal membrane excitability in the absence of one or two GJ proteins. Comparison of the three genotypes showed that Cx32 may play a dominant role in the maintenance of the CAP formation since nerves from Cx29KO mice proved to be more sensitive to the GJ blockers compared to the Cx32KO nerves showing a faster decline of the CAP amplitude. Moreover the effect of GJ blockers was similar in Cx32KO and dKO nerves. Finally, the effect of GJ blockers on the dKO nerves implies the presence of another GJ protein. In conclusion, our results confirm the direct functional involvement of Cx32 GJ channels and Cx29 hemichannels in the CAP formation and indicate the existence of at least one more connexin in peripheral nerve.

Ca(2+)-DEPENDENT ANTI-GANGLIOSIDE ANTIBODY IN SERONEGATIVE GUILLAIN-BARRÉ SYNDROME.

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Back ground: We have reported Ca^{2+}-dependent IgG anti-ganglioside GQ1b antibodies in GQ1b-seronegative patients with Fisher syndrome and its related disorders (FS-RD). In patients with FS-RD who were GQ1b-seronegative in conventional assays using phosphate-buffered saline without Ca^{2+}, 73% turned seropositive for GQ1b-related antigens in assays using Ca^{2+}-added Tris–buffered saline. ***Objective:*** We investigated whether Ca^{2+}-dependent anti-ganglioside antibodies was present also in ganglioside-seronegative patients with other clinical disease types of Guillain-Barré syndrome (GBS) other than FS-RD. ***Methods:*** The subjects were the following: 23 patients with final clinical diagnosis as GBS (acute motor axonal neuropathy [AMAN], n = 6, and acute inflammatory demyelinating polyradiculoneuropathy [AIDP], n = 17), and 5 patients with final clinical diagnosis as sensory ataxic neuropathy (SAN), n = 5. All subjects were ganglioside-seronegative in the conventional assays. We assayed serum IgG antibodies against various gangliosides (including asialo-GM1) in ELISA using Tris-buffered saline as a basal buffer in both Ca^{2+}-added and -non-added conditions. Increase of the optical density (OD) more than 0.1 in Ca^{2+}-added condition compared with Ca^{2+}-non-added one was taken significant, i.e. positive for Ca^{2+}-dependent antibody. ***Results:*** Ca^{2+}-dependent antibody was

negative in all AMAN and SAN patients. In AIDP, the antibody titers (ODs) against GaINAc-GD1a were significantly increased in 2 patients, and those against asialo-GM1 were increased in 2 other patients in Ca^{2+}-added condition. However, the titiers of those Ca^{2+}-dependent antibodies were all at low level. ***Conclusions:*** In clinical disease types of GBS other than FS-RD, Ca^{2+}-dependent IgG antibodies against ganglioside were detected in a few patients with AIDP, but the positive rate and the antibody titers were low compared with case of GQ1b-seronegative FS-RD. Ca^{2+}-dependent antibodies against ganglioside are considered to be more specific for GQ1b.

THE RELATIONSHIP BETWEEN MEDIAN SENSORY CONDUCTION OF MEDIAN NERVE AND ULNAR NERVE IN PATIENTS WITH CARPAL TUNNEL SYNDROME

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The aim of the study was to investigate the relationship between median sensory conduction of median nerve and ulnar nerve in patients diagnosed with carpal tunnel syndrome. Two hundred and eighty-six hands with carpal tunnel syndrome and 52 hands in control group were investigated. Patients were staged clinically and electrophysiologically. Diagnosis of carpal tunnel syndrome was made according to the presence of paresthesia, pain in the innervation area of the median nerve, weakness and atrophy in the median nerve innervated muscles, positive Phalen and Tinel tests. Median motor and sensorial nerve conduction study, including first, second, third finger and palm, and ulnar motor and sensorial nerve conduction of fifth finger studies were performed to all patients and control group. The ratio of distal latency and velocity of nerve conduction of first, second, third and palmar branches to fifth finger was calculated. Distal latency of first, second, third finger and palm of patients with CTS are longer and velocity is more slowly than controls. In addition to these findings, the velocity of fifth finger is also slower and distal latency of this one is longer than healthy subjects. The most sensitive method of classifying the carpal tunnel syndrome as normal, mild and moderate is the ratio of distal latency and velocity of second finger ($p<0.001$). Carpal tunnel syndrome is the most common encountered neuropathy. In nerve conduction studies can be used the ratio of distal latency and velocity of second finger as determine the degree of carpal tunnel syndrome. The most surprising finding of this report is the nerve conduction studies of fifth finger. The subclinical susceptibility of fifth finger can be explained by overusing of wrist.

RELEVANCE AND FREQUENCY OF DIFFERENT TYPES OF CHARCOT-MARIE-TOOTH NEUROPATHY IN A LARGE POPULATION OF PATIENTS STUDIED AT A SINGLE CLINICAL SITE

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Charcot-Marie-Tooth (CMT) neuropathy represents a clinically and genetically heterogeneous group of hereditary peripheral neuropathies characterized by chronic motor and sensory impairment. To date mutations in up to 80 genes may cause CMT. The aim of this study is to describe our large population of CMT patients, and, within this, highlight specific phenotypes. The CMT Clinic in Genova, started in 2004. During the years, patients underwent complete neurological, rehabilitative, neurophysiological examinations and genetic testing. The patients were routinely tested for common genes (as PMP22, GJB1, MPZ, MFN2), while in specific cases we followed the candidate gene approach testing single genes based on the genotype-phenotype correlation. However, the NGS techniques were used when routine genetic testing was negative and a clear genotype-phenotype correlation could not be identified. 679 cases are present to date in our database of CMT patients. In 185 (27.2%) patients, in spite of a clinical diagnosis of CMT, a genetic diagnosis is still lacking; 175 (25.7%) patients had alternative diagnosis (i.e hereditary spastic paraparesis etc.). Instead, in 319 patients (46.9%) a defined genetic diagnosis was reached, 180 of them being females (56.4%) and 139 males (43.5%). Among these, except for the more common CMT1A, HNPP and CMT1X phenotypes, we frequently observed patients affected by CMT1B and CMT2F. According to most literature data, we observed 21 (6.5%) patients with CMT1B and 8 patients (2.5%) affected by CMT2F. At the first visit, the CMT1B phenotype was clearly length-dependent: 71.4% patients showed impairment of the lower limbs and saving of the upper limbs; in terms of severity of the neuropathy, the mean CMTNS was 11.9 and the mean age was 48.8 years. Similarly, 75% of patients affected by CMT2F, present with the same phenotype; the mean CMTNS at the first visit was 8.1 and the mean age was 63.1 years. In conclusion, based on the experience of the Genova CMT Clinic, we describe a large population of CMT patients and a specific phenotype in CMT1B and 2F patients, characterized by involvement of the lower limbs and selective sparing of the upper ones, which may help in addressing the diagnostic algorithm.

CHRONIC NON-FREEZING COLD INJURY RESULTS IN NEUROPATHIC PAIN DUE TO A SENSORY NEUROPATHY

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Non-freezing cold injury (NFCI) develops following sustained exposure to cold temperatures, resulting in tissue cooling but not freezing. This can result in persistent sensory disturbance of the hands and feet including numbness, paraesthesia and chronic pain. Both vascular and neurological aetiologies of this pain have been suggested but remain unproven. We prospectively approached patients referred for clinical assessment of chronic pain following non-freezing cold injury between 12 February 2014 and 30 November 2016. Of 47 patients approached 42 consented to undergo detailed neurological evaluations including: questionnaires to detail pain location and characteristics, structured neurological examination, quantitative sensory testing, nerve conduction studies and skin biopsy for intra-epidermal fibre assessment. Of the 42 study participants all had experienced NFCI whilst serving in the United Kingdom armed services and the majority were of African descent (76.2%) and male (95.2%). Many patients reported multiple exposures to cold. The median time between initial injury and referral was 3.72 years. Pain was principally localised to the hands and the feet, neuropathic in nature and in all study participants associated with cold hypersensitivity. Clinical examination and quantitative sensory testing were consistent with a sensory neuropathy. In all cases large fibre nerve conduction studies were normal. The intra-epidermal nerve fibre density, however, was markedly reduced; 90·5% of subjects having a count at or below the 0·05 centile of published normative controls. Using the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) grading for neuropathic pain 100% had probable and 95·2% definite neuropathic pain. Chronic non-freezing cold injury is a disabling neuropathic pain disorder due to a sensory neuropathy. Why some individuals develop an acute painful sensory neuropathy on sustained cold exposure is not yet known but individuals of African descent appear vulnerable. Screening tools, such as the DN4 questionnaire, and treatment algorithms for neuropathic pain should now be used in the management of these patients. Funded by The Wellcome Trust and the UK Ministry of Defence

INTERNATIONAL GUILLAIN-BARRÉ SYNDROME OUTCOME STUDY (IGOS): DESCRIPTION OF THE FIRST 1000 PATIENTS

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Guillain-Barré syndrome (GBS) is highly heterogeneous regarding clinical presentation, course, electrophysiological subtype and outcome. In part this variety is associated with differences between geographical regions, although this had not been investigated in a single comparative study. One aim of IGOS is to define the influence of the geographical origin on the heterogeneity of GBS. In IGOS all GBS patients within 2 weeks of onset can participate, independent of age, variant, severity and treatment. In February 2017, 1456 patients were included from 19 countries. The first 1000 inclusions in IGOS were used in this analysis. Seventy-five patients (8%) were excluded because of alternative diagnoses (n=59, including 35 A-CIDP), protocol violations (n=5) or missing data (n=11). Of the remaining 925 patients, 60% were males and 40% female with a median age of 51 years (IQR 33-65). At entry 73% presented with tetraparesis and 11% with paraparesis. During follow-up 19% needed mechanical ventilation and 7% died. Of all GBS patients 81% received treatment (91% IVIg, 9% PE). The remaining 19% received supportive care only (mild GBS or low social-economic status).

Antecedent events were reported in 76% of patients, including upper respiratory tract infection (36%) and gastro-enteritis (26%) as the most frequent events. The pure motor form was the predominant subtype in patients from Bangladesh (69%). In Europe/Americas and Asia (without Bangladesh) the predominant subtype was the sensorimotor form (69% in Europe/Americas and 43% in Asia). In Asia (without Bangladesh) there was a relatively larger proportion of patients with MFS/MFS-overlap syndrome (22%) than in other regions (1-11%, p<0.001). The proportion of patients able to walk unaided at 12 months after follow-up was 87% in Europe/Americas, 73% in Bangladesh and 93% in Asia (without Bangladesh). Kaplan-Meier analysis comparing electrophysiological subtypes of GBS (as reported by neurologist) showed that patients with inexcitable nerves or axonal neuropathy needed more time to regain the ability to walk unaided than the patients with demyelinating or equivocal result (log-rank test, p < 0.001). These findings demonstrate the extensive geographical differences in GBS. Future IGOS studies will investigate the role of genetic and environmental factors that additionally could explain these differences.

ELECTROPHYSIOLOGICAL CRITERIA FOR GBS SUBTYPE DIAGNOSIS: A PROSPECTIVE MULTICENTRIC EUROPEAN STUDY

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This study examines whether GBS subtypes can be diagnosed by a single electrophysiological study (EDX) according to criteria by Rajabally (2014) (RA) as compared to Ho (1995) (HO) and Hadden (1998) (HA) and whether temporal dispersion (TD) parameters are helpful. Fifty-eight patients diagnosed according to Asbury and Cornblath (1990) were prospectively included between January 2015 and September 2016. EDX1 and 2 were performed 1-12 (mean=5) and 23-51 days (mean=33) after disease onset, respectively. There were no differences in classification consistency between HO and HA at EDX1 (p=0.41) and EDX2 (p=0.30), but more patients were classified as AMAN when comparing RA with HO and HA at EDX1 (p<0.01). At EDX2, RA classified more patients as equivocal with HO (p<0.001) and as AMAN with HA (p<0.001). Adding TD (≥ DCMAP or P/DCMAP duration prolongation) to RA led to an increase in AIDP at EDX1 (p=0.01) and EDX2 (0.03). There were no differences between the two EDX for HO (p=0.22), HA (p=0.75), RA (p=0.33), and RA with TD (p=0.68). Reversible conduction failure (RCF), defined as a 50% increase of the DCMAP or PCMAP at EDX2, was not related to subtypes at EDX1 (HO, Fisher's Exact Test [TE] p=0.45; RA, FE p=0.14; RA with TD; FE p=0.31) or EDX2 (HO, FE p=0.55; HA, FE p=0.30; RA, FE p=0.5; RA with TD, FE p=0.64). GM1, GD1a, GD1b and GQ1b IgG antibodies were tested (Willison, 1999; Delmont, 2015). At EDX1, only HO showed maybe more antibodies with AMAN compared to AIDP (FE p=0.02, Phi=-0.38) and with AMAN compared to equivocal cases (FE p=0.03, Phi=-0.62). At EDX2, only with HA may antibodies be more frequent with AMAN compared to AIDP (FE p=0.02, Phi=-0.40). Conclusion: Serial EDX at well-defined time intervals has no substantial effect on different GBS subtype proportions, regardless of criteria used. Since correlation with factors associated with axonal GBS, *in casu* RCF and antibodies, is far from exclusive, the usefulness of EDX subtype classification using specific criteria sets, remains doubtful. The frequency of RCF indicates that nodal/paranodal alterations may represent the main pathophysiology in more GBS patients than currently thought (Uncini and Kuwabara, 2015).

INHIBITION OF HISTONE DEACETYLASE 6 (HDAC6) PROTECTS AGAINST VINCRISTINE-INDUCED PERIPHERNAL NEUROPATHIES AND INHIBITS TUMOR GROWTH

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The most important neurological side effect of a large number of anti-cancer drugs is a painful peripheral neuropathy. Mainly chemotherapeutics that interfere with microtubules, including the plant derived vinca-alkaloids such as vincristine, are well known to cause chemotherapy-induced peripheral neuropathies (CIPN). To date, few treatments are available and focus on symptom alleviation and pain reduction rather than on preventing the neuropathy all together. For the first time, we highlight the potential of specific histone deacetylase 6 (HDAC6) inhibitors as a preventive therapy for CIPN, using novel rodent models for vincristine-induced peripheral neuropathies (VIPN), characterized by a sensory axonopathy. One reason so few therapies are available, is because the exact pathophysiological mechanisms are poorly understood. Mounting evidence proposes axonal transport, a pathway frequently disturbed in neurological disorders, as a major player in the pathophysiology of VIPN. Proper axonal transport requires dynamic microtubules which are highly modulated by post-translational modifications. Since vincristine interferes with the polymerization of microtubules, we reason disturbances in microtubule dynamics, and by extension axonal transport, could contribute to VIPN. We illustrate that increasing acetylation of α-tubulin after HDAC6-inhibition, can restore vincristine-induced defects in axonal transport in cultured dorsal root ganglion neurons. Also *in vivo,* α-tubulin acetylation was restored in the saphenous nerve and dorsal root ganglia, two sensory tissues that are affected by vincristine. Ultimately, this correlates to a reduced severity of the neurological symptoms, both on the electrophysiological and on the behavioral level. Moreover, we discovered that HDAC6-inhibition was not only protective against neurotoxicity, but also reduced tumor progression in a mouse model for acute lymphoblastic leukemia. Taken together, our results show that HDAC6-inhibition is an ideal strategy to prevent VIPN with beneficial effects both on the neurotoxicity as well as on tumor growth.

CORTICOSTEROID TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY – A MULTICENTER, RETROSPECTIVE STUDY.

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Corticosteroids are considered as one of the first line treatments for chronic inflammatory demyelinating polyneuropathy (CIDP). Different types of corticosteroids are used and there are no comparative studies assessing the improvement rates, remission rates, tolerability and the side effect profiles of these treatment regimens. In addition, there are currently no reliable predictors of favorable treatment response to steroids, which would greatly ease the choice of first line treatment. In this retrospective study we will compare efficacy, tolerability and safety of three different corticosteroid regimens used as first line treatment in three large CIDP centers in Netherlands, Serbia and Italy. Treatment naïve CIDP patients who received either pulsed dexamethasone, pulsed methylprednisolone or daily prednisone will be included in the study. Data will be extracted from patient charts. The primary outcome is the percentage of treatment responders at 6 months after start of first treatment, in which treatment response is defined as subjects who improved after treatment and are either without treatment after six months or are still being treated with the first chosen therapy. Secondary endpoints include the remission rates and in case of a relapse, the mean duration of remission to relapse; the discontinuation rate within 6 months of treatment due to inefficacy, adverse events or intolerance; and the frequency of adverse events and serious adverse events (SAE) during treatment or within 1 month after stopping treatment. Furthermore, we will explore the value of previously reported potential predictors of treatment response. Results will be presented at the Peripheral Nerve Society Meeting 2017.

EXPANDED B-CELL RECEPTOR CLONES ARE PRESENT IN PERIPHERAL BLOOD SAMPLES IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

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Following reports that pathogenic antibodies are present in a minority of patients with chronic demyelinating inflammatory neuropathy (CIDP), we studied whether oligoclonal expansions of B-cell clones are present in patients with CIDP. Recently, we developed a new method for B-cell receptor (BCR) repertoire landscaping based on high throughput sequencing (HTS) of RNA extracted from blood. BCR repertoire was analyzed in 30 patients with CIDP: 10 patients with active disease and starting treatment (group 1), 10 patients with stable disease using intravenous immunoglobulin (IVIg) treatment in which treatment withdrawal was attempted (group 2), and 10 patients in remission (i.e. no treatment in the last 12 months, group 3). Clinical parameters and sampling was performed at baseline (group 1, 2 and 3), at 6 months after start of treatment (group 1), at 6 months or earlier in case of relapse in group 2 and at baseline only in group 3. Most CIDP patients had highly expanded BCR clones,

regardless of disease activity and response to treatment. However, in group 1, the most expanded B-cell clones at baseline showed no overlap with the expanded BCR clones after improvement. Based on these preliminary data expanded BCR clones are observed in the peripheral blood of most CIDP patients, regardless of disease activity (active, stable disease or remission/cure). Functional characterization of these expanded clones remains to be performed.

FREQUENCY AND ACTIVATION STATUS OF MYELOID CELLS IN THE GUILLAIN-BARRÉ SYNDROME

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Myeloid cells, including monocytes, macrophages and dendritic cells, are critically involved in the induction of adaptive immune responses, clearance of pathogens and in the initiation of tissue repair. In the Guillain-Barré syndrome (GBS), macrophages are present in the peripheral nerve, where they phagocytose (damaged) myelin and axons. Dendritic cells (DC) are increased in the cerebrospinal fluid of patients with GBS. However, the composition and phenotype of monocytes and DC subsets in the peripheral blood is unclear and it is unknown if these cells can be used as biomarker to monitor disease activity or response to treatment. Here we investigated the frequency and phenotype of six myeloid subsets in the peripheral blood mononuclear cells (PBMC) using advanced 13-color flow cytometry. PBMC were isolated from 20 patients with GBS, before and after immunomodulatory treatment, and 20 age and gender-matched, healthy controls. The frequency of total monocytes, determined as percentage of CD45+ cells, was increased in GBS patients compared to controls ($p<0.05$). The monocyte population was skewed towards more intermediate (CD14+CD16+; $p<0.05$) and less non-classical (CD14-CD16+; $p<0.01$) monocytes. Classical (CD14+CD16-) and intermediate monocytes as well as CD1c+ DC expressed significantly higher levels of CD38 compared to healthy controls. In contrast, the expression of CD40 and Siglec-7 was significantly higher in the non-classical monocytes of GBS patients compared to controls. No differences were observed in the expression of CD69, CD80, CD83 and Siglec-1. Immunomodulatory treatment strongly reduced the frequency of non-classical monocytes and all DC populations in CD45+ PBMC. The expression of CD40, CD1c and HLA-DR was reduced in classical monocytes after treatment. In addition, Siglec-7 expression was reduced in several monocyte and DC populations after treatment. In summary, our data identify significant changes in the monocyte compartment in GBS. The decrease in non-classical monocytes may suggest that these cells have migrated to peripheral tissues, promoting the differentiation of classical monocytes into intermediate monocytes. Further analysis should reveal whether these changes are related to preceding infections, disease severity and response to treatment.

SUBCUTANEOUS IMMUNOGLOBULIN FOR MAINTENANCE TREATMENT IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP), A MULTICENTER RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL: THE PATH STUDY

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Approximately two-thirds of CIDP subjects need long-term corticosteroids or intravenous immunoglobulins (IVIg), with IVIg being slightly preferred based on safety profiles. Subcutaneous Ig (SCIg) is an alternative option for Ig delivery but has not previously been investigated in a large-scale clinical trial in CIDP.
We performed a randomized, double-blind trial in CIDP investigating 0.2 and 0.4 g/kg weekly doses of SCIg IgPro20 (Hizentra®, CSL Behring) versus placebo in 172 subjects for maintenance treatment. IVIg-dependent adults with definite or probable CIDP according to EFNS/PNS criteria were eligible. The primary outcome was the percentage of subjects with a CIDP relapse (1-point deterioration on adjusted INCAT disability score) or who were withdrawn for any other reason during the 24-week SCIg-treatment period. Multiple secondary endpoints were assessed. Superiority of at least one IgPro20 dose over placebo was tested one-sided using the Cochran-Armitage trend test for the primary outcome and the Jonckheere-Terpstra tests for secondary outcomes.
The primary outcome occurred in 33% of high-dose SCIg, 39% of low-dose SCIg, and 63% of placebo subjects ($p < 0.001$); CIDP relapse occurred in 19% of high-dose SCIg, 33% of low-dose SCIg and 56% of placebo subjects ($p < 0.001$), respectively. Both SCIg doses were superior to placebo (low-dose vs placebo $p = 0.007$; high dose vs placebo $p < 0.001$). Median INCAT score, MRC sum score, and grip strength remained stable in SCIg subjects. High-dose

SCIg prevented the R-ODS decline seen with low-dose SCIg and placebo ($p < 0.001$). All placebo subjects deteriorated on measures of strength and disability.
Causally related adverse events occurred in 47 (27%) subjects (18% placebo, 30% low dose, and 35% high dose).
SCIg IgPro20 was efficacious and safe as maintenance treatment. High-dose and low-dose SCIg were both superior to placebo, with the high dose potentially showing better efficacy.
Funding: CSL Behring sponsored the study
Trial Registration: Clinicaltrials.gov, number NCT01545076.

CHARCOT-MARIE-TOOTH DISEASE TYPE-2 ASSOCIATED WITH TWO MISSENSE MUTATIONS IN MME GENE

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Mutations in metalloendopeptidase (*MME*) gene have been associated with autosomal-recessive late-onset Charcot-Marie-Tooth type-2 (CMT2). To date, all patients have had at least one truncating mutation, either in homozygosity or in trans with a missense mutation. More recently, loss-of-function and missense heterozygous mutations were also identified in autosomal-dominant CMT. We report the case of a previously healthy Caucasian woman, born to healthy unrelated parents, who presented at the age of thirty-nine with numbness and cold sensation in the lower limbs. Subsequently she developed progressive gait disturbance and impaired hand dexterity. Her homozygous twin presented at the same age with similar symptoms. The family history was otherwise uneventful, in particular neither neuropathy nor dementia were described. Neurological examination at the age of fifty-three revealed a steppage gait, distal upper and lower limb atrophy and weakness, distal sensory loss and bilateral pes cavus. Deep tendon reflexes were normal in the upper limbs and absent in the lower limbs. Nerve conduction studies revealed an axonal sensory and motor neuropathy. A sural nerve biopsy revealed a reduction in myelinated nerve fibers and active axonal degeneration. Targeted Sanger sequencing of *MPZ*, *GJB1*, *GDAP1*, *NEFL*, *FKRP*, *BSCL2*, *HSPB8* and *MFN2* were negative. SureSelect Focused Exome sequencing was therefore performed and identified two missense heterozygous mutations [c.263G>A,p.C88Y;c.1279T>C,p.Y427H] in *MME*. The two mutations were absent from control databases (e.g. Exac), affected highly conserved aminoacids and were predicted to have deleterious effects by in silico analysis. Unfortunately, both parents were deceased and we were therefore unable to prove that the two mutations reside on separate alleles. *MME* encodes the metalloprotease neprilysin whose role in peripheral nervous system is still unclear. Higuchi and colleagues have described 10 Japanese CMT2 families with late-onset sensory-motor axonal neuropathy and recessive loss-of-function mutations in *MME*. We report two novel missense mutations in *MME* in a case of late-onset CMT2. We hypothesize an autosomal-recessive mode of inheritance as most likely given the clinical phenotype and the absence of a family history.

EFFICACY OF CYCLOPHOSPHAMIDE IN ANTI-CONTACTIN-1 ANTIBODIES ASSOCIATED TO CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY AND MEMBRANOUS GLOMERULONEPHRITIS: A CASE REPORT

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Anti-contactin-1 (CNTN1) antibodies were recently identified in a subgroup of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) showing acute/subacute onset of severe sensory-motor neuropathy and poor response to intravenous immunoglobulin (IVIg) and corticosteroids. These antibodies belong to the IgG4 isotype and interact with CNTN1-neurofascin 155 (NF155) complex at paranodes leading to loss of nodal integrity. A 59-year-old man presented with acute onset of distal weakness in the lower limbs, four limbs paraesthesias and sensory ataxia. At clinical examination ankle swelling was also observed. Nerve conduction study showed a demyelinating polyneuropathy and cerebrospinal-fluid examination revealed cyto-albuminologic dissociation. Sural nerve biopsy disclosed diffuse loss of myelinated fibres. At routine blood test serum albumin was reduced and proteinuria was 10 gr/24 hours, thus leading to the diagnosis of nephrotic syndrome. Kidney biopsy showed changes consistent with membranous glomerulonephritis, together with sub-epithelial deposits of immune complexes and complement deposition. Treatment with IVIg and corticosteroids did not improve neurological status, while membranous glomerulonephritis showed moderate response to IVIg. A six-month course of cyclophosphamide was started leading to normalization of renal function and muscle strength and partial improvement of sensory ataxia. The patient did not require any further treatment and after 10 years his condition remains stable. CNTN1 antibodies were tested on a recently collected

patient's serum and resulted positive on both ELISA and cell-based assay. The patient here reported showed the typical clinical features of anti CNTN1-associated CIDP including older age, acute onset, severe motor impairment and sensory ataxia. The contemporary occurrence of membranous glomerulonephritis was reported in only one other case. Contactin-1 is expressed at low levels in the kidney and a direct damage of anti-CNTN1 antibodies could be hypothesized. Alternatively, renal damage might have been secondary to unspecific immune complexes deposition. A good response to anti-CD20 rituximab was recently reported in patients with CIDP associated with anti-CNTN1 and anti-NF155 antibodies. Notwithstanding this single-case observation, our report suggests that also cyclophosphamide may be considered an effective therapy in anti-CNTN1 antibodies-associated CIDP and membranous glomerulonephritis, leading to persistent clinical remission.

DULOXETINE IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY.

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Duloxetine is the only agent demonstrated effective in treating pain related with chemotherapy-induced peripheral neuropathy (CIPN). Patients with symptomatic CIPN treated with duloxetine were retrospectively collected in a single-institution. Aim of the study was to evaluate the drug's efficacy and rate of compliance. Only patients with CIPN with distressing positive symptoms (pain, numbness and/or paresthesia), and non-progressive disease were included. CIPN was graded employing the Total Neuropathy Score (TNS©) and National Cancer Institute-Common Toxicity Criteria. Response to duloxetine was assessed with Patient Global Impression of Change (PIGC) scale (1: no benefit; 7: excellent response). Consecutive first one-hundred CIPN patients treated with duloxetine were analyzed. Median age was 62 (29-81). 59, 37, 2 and 2 received platinum, taxane, bortezomib and vincristine-based regimen, respectively. Median TNSc© was 9 (1-17). Severity of neuropathy was grade 1 (20%), grade 2 (66%), and grade 3 (14%). Sixteen patients were on treatment with other analgesic agents. Median time from finishing chemotherapy to duloxetine initiation was 6 months [0-63]. Median PIGC score was 3 [1-7]. Among responders, 45.5% and 54.5% scored low (2-4) and high (5-7) benefit, respectively. Fifty-seven (57%) patients discontinued early duloxetine due to intolerable side effects (n=37) or lack of efficacy (n=20). Most frequently reported adverse events were cognitive (26%), gastrointestinal (14%) and genitourinary (9%). Discontinuation due to perception of lack of efficacy was more frequently reported by men (75% vs 25% p=0.001). Women presented higher punctuations on PIGC scale compared with men (3.8±2.1 vs 1.9±1.7, p=0.005). PIGC scores were significantly higher in patients receiving taxane (3.8±2.4) than platinum (2.5±1.9) agents (p=0.027). No significant differences according severity of neuropathy neither type of chemotherapy were observed in drop-out and retention rates. Patients with long-lasting CIPN (> 6 months) reported lower PIGC scores (2.1±1.7 vs 3.7±2.3, p=0.008) and higher frequency of suspension due to adverse events (22% vs 15%, p=0.039) and less rate of continuation of duloxetine (12% vs 26%, p=0.024). More than one-third of patients with disturbing CIPN discontinued duloxetine prematurely due to intolerable side-effects. Low tolerability, male gender and long-lasting CIPN may limit duloxetine usefulness in the treatment of symptomatic CIPN.

IMMUNOGLOBULIN TREATMENT FOR PATIENTS WITH MILD GUILLAIN-BARRÉ SYNDROME: AN INTERNATIONAL PROSPECTIVE OBSERVATRIONAL STUDY

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The efficacy of intravenous immunoglobulin (IVIg) in Guillain-Barré syndrome (GBS) has only been demonstrated in severely affected patients who are unable to walk independently. Although there is no proof that IVIg is effective in milder forms of GBS, some neurologists are treating these patients with IVIg considering that even milder forms of GBS may result in poor recovery, residual deficits, fatigue or pain.

We determined the effectiveness of a single course of IVIg (2 g/kg in 2-5 days) in relatively mild forms of GBS in the ongoing observational International GBS Outcome Study (IGOS). The GBS disability score, MRC sum score and patient reported outcome measures (PROM) were compared at 4 and 26 weeks. Ordinal logistic regression analysis was used to determine the effect of IVIg on the GBS disability score, adjusted for previously identified prognostic factors.

Data were analyzed from the first 1300 patients enrolled in IGOS by December 2016, including 238 patients with mild GBS at entry, of which 68 patients (29%) were treated with supportive care, while 170 patients (71%) received IVIg (start IVIg after onset of symptoms in days, median 6, IQR 4-9). At baseline, patients in the IVIg treated group compared to the untreated group less frequently had pure motor GBS (10% versus 31%, p<0.001) and axonal damage or

unresponsive nerves (7% versus 19%, p=0.032), but a worse GBS disability scores at nadir (p=0.005). The adjusted common odds ratio for a better GBS disability score at 4 weeks was 2.81 (95% CI 1.34-5.89). At 4 weeks, the median MRC sum scores and PROM were not significantly different between treated and untreated patients. However, more patients in the IVIg group showed complete recovery of muscle strength at 4 weeks than patients in the control group (71% versus 53%) (p=0.01) and more frequently showed full neurological recovery on the GBS disability scale (13% versus 3%, p=0.03). Additional results will be presented at the conference. Based on the results of this interim analysis in observational data, we conclude that patients with a relatively mild form of GBS may benefit from a single course of IVIg.

INTERNATIONAL SECOND IMMUNOGLOBULIN DOSE IN PATIENTS WITH GUILLAIN-BARRÉ SYNDROME WITH POOR PROGNOSIS (I-SID GBS), A PROSPECTIVE OBSERVATIONAL STUDY.

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Despite treatment with intravenous immunoglobulin (IVIg), many patients with Guillain-Barré syndrome (GBS) recover insufficiently. We primarily aimed to determine whether a second IVIg course (2 g/kg in 2-5 days) in patients with a poor prognosis improves outcome on the GBS disability scale after 4 weeks. We included patients from the prospective, observational International GBS Outcome Study (IGOS) treated with IVIg and who had a poor prognosis on the modified Erasmus GBS Outcome Score (mEGOS). Of 1300 patients enrolled in IGOS, 239 patients were eligible; 200 patients (84%) were treated with one IVIg course (control group); 19 patients (8%) received an 'early' second IVIg course (1-2 weeks after start first course) and 20 patients (8%) a 'late' second IVIg course (within 2-4 weeks). One week after study entry, patients receiving an 'early' or 'late' second IVIg course had significantly worse GBS disability scores and MRC sum scores than controls, implying the need for adjustment of baseline characteristics. The adjusted common odds ratio for a better GBS disability score at 4 weeks was 0.69 (95% CI 0.19-2.42) for the 'early' group, and 0.51 (95% CI 0.15-1.73) for the 'late' group, suggesting worse outcomes with a second course of IVIg compared to controls. At 6 months, 10 patients (71%) in the 'early' second IVIg group, 100 patients (65%) in the control group and only 2 (18%) in the 'late' second IVIg group were able to walk unaided (p=0.006). The adjusted common odds ratio for a better GBS disability score at 26 weeks was 1.66 (95% CI 0.44-6.21) for the 'early' second IVIg group and only 0.53 (95% CI 0.14-1.96) for the 'late' second IVIg group. In GBS patients with a poor prognosis, we did not find a beneficial effect of a second course of IVIg after 4 weeks follow-up. Our results suggest that an 'early' administered second IVIg course might improve outcome at 26 weeks. Given the limitations of this observational study, a randomized controlled trial with a larger number of GBS patients with a poor prognosis being treated early in the disease course is needed to confirm or refute these results.

ATYPICAL MULTIFOCAL MOTOR NEUROPATHY WITH SCAPULAR WINGING

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Multifocal motor neuropathy (MMN) is an inflammatory demyelinating chronic neuropathy characterized by progressive asymmetric weakness in the distribution of two or more peripheral nerves, without objective sensory loss or upper motor neuron signs. The cardinal neurophysiological finding is conduction block outside the usual sites of nerve compression. Supportive clinical criteria include high titers of anti-GM1 antibodies, good response to IVIg, increased cerebrospinal fluid (CSF) protein (<1g/dL) and magnetic resonance imaging (MRI) with diffuse swelling of the brachial plexus. We report a case of a 31 year old woman with a two month history of progressive muscular weakness which began in the right upper extremity, described as difficulty in gripping objects, writing and typing on the computer, followed by progressive lower extremity weakness with difficulty rising from a chair and left foot drop. She also complained of pain in her right trapezius and scapular area. She denied any tingling or numbness. On neurological examination there was right scapular winging and asymmetric weakness predominantly involving the right upper and left lower extremities. Reflexes were absent throughout. Lumbar puncture revealed albuminocytological dissociation (WBC 0 and protein 1.13 g/dL). NCS revealed slow conduction velocities for both ulnar and median nerves and a median nerve conduction block at the forearm segment. Sensory nerve action potentials were normal for all tested nerves. Needle EMG revealed acute denervation of right periscapular muscles. Brachial plexus MRI showed symmetric bilateral thickening from trunks to peripheral nerves. Anti-GM1 IgG/IgM were negative. Two days after lumbar puncture and the beginning of IVIg, patient presented binocular diplopia on extreme left lateral gaze. Brain MRI with and without contrast showed no intracranial pathologies. After five days of IVIg, patient was discharged with significant clinical improvement and recovery of the right scapular winging. Diplopia improved a week after discharge.

We report an atypical multifocal motor neuropathy case. Although this patient fulfills all clinical criteria for MMN, we report some features usually not found in MMN such as scapular winging and a mild and transient left VI nerve palsy. MMN should be included in the differential diagnosis of scapular winging.

SENSORY PHENOTYPE AND RISK FACTORS FOR PAINFUL DIABETIC NEUROPATHY: A CROSS SECTIONAL OBSERVATIONAL STUDY

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Despite many studies addressing biomarkers for pain in diabetic polyneuropathy (DPN), little is known about why it affects only a certain proportion of DPN patients. The somatosensory system plays a key role in the pathophysiology of neuropathic pain (NeuP) and subgroups with different sensory profiles might respond differently to pain treatment. We aimed to characterize sensory phenotypes of patients with painful and painless diabetic neuropathy and to assess demographic, clinical, metabolic, electrophysiological and psychological parameters related to the presence of NeuP in a large cohort of well-defined DPN subjects.
This observational cross-sectional multi-centre cohort study (performed as part of the ncRNAPain EU consortium) of 232 subjects with DPN (non-painful, nDPN, n=74; painful, pDPN n=158) associated with diabetes mellitus of type 1 and 2 (median age 63 years, range 21-87 years; 92 women) comprised detailed history taking, neurological examination, laboratory tests, quantitative sensory testing, nerve conduction studies, neuropathy severity scores, and neuropsychological questionnaires. All parameters were analysed with regard to the presence and severity of NeuP. The presence and severity of NeuP were positively correlated with severity of neuropathy and thermal hyposensitivity ($p<0.001$). A minority of pDPN patients (14.6%) had a sensory profile indicating thermal hypersensitivity; this was associated with less severe neuropathy and better response to pain therapy. The presence of NeuP was also associated with female gender ($p<0.001$) and with higher cognitive appraisal of pain as assessed by the pain catastrophizing scale ($p<0.001$), while parameters related to diabetes (duration, HbA1c, microangiopathy) showed no influence on NeuP presence and severity. This study confirms the necessity of comprehensive DPN phenotyping and underlines the importance of the severity of neuropathy that should be taken into account in the stratification of patients with pDPN for analgesic treatment and drug trials.

EVALUATING THE BENEFITS OF COMMUNITY BASED AEROBIC TRAINING ON THE PHYSICAL HEALTH AND WELL-BEING OF PEOPLE WITH CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: A PILOT RANDOMISED CONTROLLED TRIAL

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People with Charcot Marie Tooth disease (CMT) experience slowly progressive muscle weakness, sensory loss and musculoskeletal changes over time. This leads to disability and risk of comorbidities due to inactivity. Exercise is important to maintain general health but may also help to improve symptoms of CMT. We conducted a randomised controlled crossover trial of aerobic exercise to ascertain the effect of training on fitness levels, muscle strength, function and general well-being. In addition, we monitored the safety of training and feasibility of participation in this type of exercise in local community gyms. Motivation, confidence and barriers to exercise were explored using qualitative interviews. The recruitment target was 30 people. In total 282 people with CMT 1A were approached to participate and 191 were unable to commit to the trial or did not meet the study criteria on initial screening. Thirty-one people underwent more detailed screening but three failed to meet the study criteria, five people withdrew before starting and three withdrew part way through the study. The data for the 23 people who started the study were analysed using a random effects model. There was a 76% participation level in the training and it was well tolerated with no increases in pain or blood serum creatine kinase. An increase in VO2peak (ml/min/kg) was observed in the CMT group with (pre training: n=21, 22.28 ±4.43, 95% CI 20.57 to 24.28; post training: n=21, 24.52 ±4.40, 95% CI 22.62 to 26.33; pre control: n=18, 22.67 ±5.29 95% CI 20.22 to

25.05; post control: n=18, 22.94 ±4.22, 95% CI 21.00 to 24.83). There was wide between subject variation leading to a small overall effect size with Cohen d of 0.1302785 (95% CI:-0.33 to 0.59). A tentative regression model showed no effect of group or time point. There were no major changes in other measures of impairment, function or patient reported outcome measures. This pilot study showed that a community based model of training had a small effect on cardiopulmonary fitness, and was well tolerated with good participation.

PMP22 EXON 4 DELETION CAUSES ER RETENTION OF PMP22 AND A GAIN-OF-FUNCTION ALLELE IN CMT1E

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The goal of this study was to determine whether predicted fork stalling and template switching (FoSTeS) during mitosis deletes exon 4 in peripheral myelin protein 22 KD (PMP22) and causes a gain-of-function mutation associated with peripheral neuropathy in a family with Charcot Marie Tooth disease type 1E. Two siblings previously reported to have genomic re-arrangements predicted to involve exon 4 of *PMP22* were evaluated clinically and by electrophysiology. Skin biopsies from the proband were studied by RT-PCR to determine the effects of the exon 4 re-arrangements on exon 4 mRNA expression in myelinating Schwann cells. Transient transfection studies with wild type and mutant PMP22 were performed in Cos7 and RT4 cells to determine the fate of the resultant mutant protein. Both affected siblings had a length-dependent demyelinating neuropathy with severely slow nerve conduction velocities (< 10 m/sec). RT-PCR studies of Schwann cell RNA from one of the siblings demonstrated a complete in frame deletion of *PMP22* exon 4 (PMP22delta4). Transfection studies demonstrated that PMP22delta4 protein is retained within the endoplasmic reticulum and not transported to the plasma membrane. Our results confirm that that FoSTeS mediated genomic rearrangement produced a deletion of exon 4 of PMP22, resulting in expression of both PMP22 mRNA and protein lacking this sequence. In addition, we provide direct experimental evidence for endoplasmic reticulum retention of the mutant protein suggesting a gain-of-function mutational mechanism consistent with the observed CMT1E in this family. PMP22delta4 is another example of a mutated myelin protein that is misfolded and thus likely to contribute to the pathogenesis of the neuropathy.

BLINK R1 LATENCY UTILITY IN DIAGNOSIS AND TREATMENT ASSESSMENT OF POEMS AND CIDP

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In POEMS and CIDP, distal limb nerve conduction studies are limited in identifying demyelination and detecting treatment effects in severely affected patients. Blink reflex R1 latency may help to not only identify demyelination but also provide a meaningful treatment outcome measure especially in severely affected patients. POEMS and CIDP patients having undergone routine nerve conductions and blink reflex testing were identified. Correlation between R1 latency, limb nerve conduction studies and neuropathy impairment scores (NIS) was calculated with treatment. Blink reflexes were performed in 182 patients (124 POEMS, 58 CIDP; NIS range: 12-145 points). Overall, R1 latency prolongation occurred in 64.3% of patients (65.3% POEMS, 62.1% CIDP). Patients with R1 prolongation (>13ms) had more severely affected nerve conductions in both POEMS (ulnar CMAP 2.6mV vs 4.5mV, p=0.001) and CIDP (ulnar CMAP 2.0mV vs 6.1mV, p< 0.001). R1 latency correlated with NIS severity in POEMS better than CIDP (R^2=0.24 vs 0.10, p=<0.001 vs. 0.014). Follow-up NIS and R1 latency evaluations after treatment were available in 31 patients (16 POEMS, 15 CIDP). The R1 latency changes were concordant with the NIS changes in 94% of POEMS and 60% of CIDP patients. In severely affected patients [ulnar CMAP amplitude ≤0.5mV (9.9%: 18/182)] except for one, all had prolonged R1 (>13ms), allowing for treatment follow up and initial diagnosis. Blink reflex R1 latencies are valuable in defining demyelination in severely affected POEMS and CIDP patients, but also provide a sensitive, early treatment outcome measure among those same severely affected patients.

INTRAVENOUS IMMUNOGLOBULIN THERAPY FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN PEDIATRIC PATIENTS: AN OBSERVATIONAL STUDY

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Chronic inflammatory demyelinating polyneuropathy (CIDP) rarely occurs in children. Clinical trials in pediatric patients have not been performed and there

are little data on therapy with intravenous immunoglobulin (IVIG). We performed an observational trial to investigate the risk of Adverse Events of Special Interest (AESI) with IVIG, i.e. hemolytic anemia, aseptic meningitis, acute renal failure, thromboembolic events and anaphylactic reactions. The study cohort was derived from the US Premier Perspective database and consisted of patients <18 years with a diagnosis of CIDP (ICD-9 CM diagnosis Code 357.81) treated with the IVIG Privigen® (CSL Behring, Bern Switzerland) between Jan 2008 and Dec 2015. We identified 17 pediatric CIDP patients: 3 preschool children (age 2–5 years at first treatment for CIDP), 6 children (6–12 years) and 8 adolescents (13–18 years); 9 females and 8 males; 14 white, one black and two allocated to "other race". Six patients had a history of other IVIG use for Guillain-Barré syndrome, one patient for myasthenia gravis and one for immunodeficiency before the diagnosis of CIDP. The mean Privigen® dose calculated from the cumulative quantity of Privigen® per treatment episode and the corresponding age- and gender specific median of the US population body weight estimate was 1.3 g/kg body weight. The number of recorded treatment episodes per patient ranged from 1 to 21. Using an at-risk period of 30 days for hemolytic anemia, and 10 days for other AESI after each Privigen® administration, no AESI were observed in the 17 patients with CIDP with a total of 3720 person-days at-risk for HA and 1380 person-days at-risk for other AESI. This observational study shows that IVIG (Privigen®) is used for treatment of CIDP in pediatric patients with or without concomitant conditions and revealed no particular safety issues in this patient group.

MITOCHONDRIAL DYSFUNCTION AND ABNORMAL CALCIUM HANDLING IN CELLULAR MODELS OF HEREDITARY SENSORY NEUROPATHY TYPE 1

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HSN-1 is a peripheral neuropathy most frequently caused by missense mutations in the SPTLC1 or SPTLC2 genes, which code for two subunits of the enzyme serine palmitoyltransferase (SPT). SPT catalyzes the first and rate limiting step of de novo sphingolipid synthesis. It has been shown that mutations in SPT cause a change in enzyme substrate specificity which results in the production of two atypical sphinganines, deoxysphinganine (DSp) and deoxymethylsphinganine (DMSp), rather than the normal enzyme product, sphinganine (Sp). Levels of deoxysphingolipids are elevated in the blood of HSN-1 patients and this has been shown to cause the peripheral nerve damage characteristic of the disease, which affects both sensory as well as motor axons. However, the underlying pathomechanism of how deoxysphingolipids damage neurons remains elusive. Here, DSp and DMSp-mediated neurotoxicity was examined in primary mouse motor and sensory neurons, by assessing cell survival and neurite outgrowth following exposure to different concentrations of Sp, DSp or DMSp. The abnormal enzyme products were found to have a rapid and dose-dependent neurotoxic effect in primary neurons. We also explored the potential mechanisms that underlie deoxysphingolipid neurotoxicity, by characterizing mitochondrial function and changes in calcium handling. We found that mitochondrial dysfunction and calcium handling deficits may be key mediators of abnormal sphingolipid neurotoxicity, in both motor and sensory cell models. Specifically, we revealed mitochondrial abnormalities, signs of endoplasmic reticulum stress and dysfunction of store-operated calcium channels. We propose that early deficits in mitochondria and calcium handling may underlie deoxysphingolipid neurotoxicity and thus present potential therapeutic targets for HSN-1.

GAIT PATTERNS OF CHILDREN WITH CMT TO INFORM THE DESIGN OF 3D PRINTED ORTHOSES

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Ankle-foot orthoses (AFO) are commonly prescribed for children with Charcot-Marie-Tooth disease (CMT) to manage foot drop, however the type and severity of functional impairment results in gait deviations that might require alternate orthotic designs. The aim of this study was to identify 3D gait patterns of children with CMT based on severity of functional weakness (based on heel walk, toe walk and foot drop items during gait using the CMT Pediatric Scale) to inform a design pipeline for 3D printed orthoses. 3D gait data were captured with an 8-camera Vicon Nexus motion capture system using the lower body Plug-in-Gait model in 60 children with CMT (34 male; 11±3.1yrs, 147±16.8cm, 44±17.4kg), of various CMT types: 47 CMT1A, 1 CMT1E, 2 CMT1F, 1 CMT2A, 2 CMT 4C, 4 CMTX1, 3 CMTX3 and compared to 50 typically developing children (15 male; 9.8±3.8yrs, 140±19.6cm, 9±19.0kg). Data were subdivided into three groups denoting increasing severity of dorsiflexion and plantarflexion weakness: no difficulty heel or toe walking (CMT_{ND}), difficulty heel walking (CMT_{DH}), difficulty toe and heel walking (CMT_{DTH}). The CMT_{ND} group showed a near-normal gait pattern. The only significant differences noted at the ankle were reduced peak dorsiflexion in stance ($p<0.05$), indicating that an orthotic intervention may not be required. In addition to reduced peak dorsiflexion, the CMT_{DH} group demonstrated significantly reduced dorsiflexion in swing (foot-drop) and a reduced dorsiflexor moment in loading response ($p<0.001$). This suggest, the CMT_{DH} group would require a flexible AFO to allow activation of the plantarflexors during push-off, prevent foot-drop and restore a heel

rocker in loading response. In contrast, the CMT_{DTH} group presented with significantly delayed and increased peak dorsiflexion in stance and reduced plantarflexion and power at push-off ($p<0.05$). They also had significantly increased mean knee extensor moment ($p<0.05$) revealing early signs of 'crouch gait'. Therefore, the CMT_{DTH} group would require a rigid AFO to limit the amount of dorsiflexion and assist movement of the ground reaction force anterior to the knee during stance. Three distinct gait patterns at the ankle were identified in children with CMT, indicating patient-specific orthotic design pathways to target specific functional impairment.

3D PRINTING ANKLE-FOOT ORTHOSES FOR CHILDREN WITH CMT: A REVIEW OF THE LITERATURE

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Children with CMT are often prescribed ankle-foot orthoses (AFO) to manage lower limb impairment such as foot drop and foot deformities. They are handmade by plaster cast followed by thermoplastic moulding. This traditional approach provides limited design options, can be costly, with long outpatient wait times. 3D printing, also known as additive manufacturing, has the potential to transform the way orthoses are prescribed, designed and manufactured. The aim of this review was to evaluate the evidence of 3D printing AFOs compared to traditional manufacturing methods, for children with CMT. There are currently no studies evaluating the application of 3D printing AFOs for children with CMT. However, a small, but emerging evidence base exists for 3D printed AFO's in adults from studies including healthy participants and populations with rheumatoid arthritis, post-polio syndrome, foot drop and ankle weakness secondary to injury. Samples sizes ranged from 7-38 participants for studies related to in-shoe orthoses and from 1-10 for studies related to AFOs. The methods of 3D printing included sterolithography, selective laser sintering and fused deposition modelling using materials such as nylon 11, nylon 12, polylactide, polycarbonate and ABS. 3D printed AFOs were comparable to traditional manufactured orthoses in terms of patient-perceived comfort, temporal-spatial parameters, plantar pressure measurements and 3D gait analysis. However, the effects of long-term usage and durability of 3D printed AFOs has not been investigated. 3D printing orthoses have potential advantages including increased design possibilities, improved productivity, higher compliance, and reduced labour needs. Disadvantages include redesigning clinical pathways, limited evidence base for clinical effectiveness, limited biocompatible materials, occupational safety considerations and a high level of expertise required for software operation and fabrication of devices. Further research is required to determine the feasibility of 3D printed AFOs for children with CMT, and the most appropriate and effective printing pathway, materials to improve health outcomes of affected patients.

TREATMENT INDUCED NEUROPATHY OF DIABETES IN PATIENTS WHO HAVE UNDERGONE BARIATRIC SURGERY

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Treatment-Induced Neuropathy of Diabetes mellitus (DM) (TIND) is a complication of rapid glycaemic control. Individuals present with neuropathic pain and autonomic dysfunction within 8 weeks of improvement in glucose control. The use of both insulin and oral hypoglycaemic agents has been associated with TIND. Its severity is determined by the rate and quantum of HbA1c decline. Other predisposing factors include anorexia and weight loss. We studied the incidence of TIND in DM patients who have undergone massive weight loss and HbA1c decline after bariatric surgery. We screened electronic records of 159 patients (74 DM, 85 non-DM) who underwent bariatric surgery between 2012 and 2015. 14 DM patients fulfilled the TIND HbA1c criteria of a decrease of ≥2% over 3 months or ≥4% over 6 months. One patient was excluded because the decrease in HbA1c was not contemporaneous with weight loss. The mean and median decrease in BMI per month was 2.01 and 1.82 respectively. The mean and median interval between surgery and decrease in HbA1c was 88.2 and 89.5 days respectively. Records of these 14 patients were scrutinized and classified as: 'Probable TIND': acute painful neuropathy AND acute dysautonomia WITH temporal relationship to the decrease in HbA1c; 'Possible TIND': acute painful neuropathy OR acute dysautonomia OR temporal relationship to decrease in HbA1c is uncertain; 'Unlikely TIND': when an alternative explanation exists for symptoms. Only one patient was classified as 'Possible TIND': A 50-year-old woman who developed neuropathic pain in both lower limbs 1 month after a rapid HbA1c decline of 5.2% and about 5 months after bariatric surgery. She had no documented autonomic symptoms. Our study is limited by small cohort size, retrospective design and reliance on hospital records. Nonetheless, it demonstrates that besides nutritional neuropathies, TIND should also be considered in DM patients who develop peripheral neuropathy after bariatric surgery. In another study, we found TIND is uncommon in a general cohort of diabetic patients. The occurrence of 1 'Possible TIND' in only 14 DM patients corroborates earlier data that weight loss may act in tandem to increase the risk of TIND.

TRPV4-MEDIATED DISRUPTION OF CALCIUM SIGNALING AND

MITOCHONDRIAL AXONAL TRANSPORT IN A DROSOPHILA MODEL OF CMT2C

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Dominant missense mutations in the gene encoding the cation channel transient receptor *vanilloid*, family member 4 (TRPV4) cause inherited neuropathies including Charcot-Marie-Tooth disease 2C (CMT2C). *in vitro,* mutations in TRPV4 that cause CMT2C cause a gain of TRPV4 channel function and increased intracellular calcium which subsequently leads to cellular toxicity. However, the mechanisms by which CMT2C mutations in TRPV4 lead to neuronal dysfunction *in vivo* remain poorly understood. We generated transgenic *Drosophila* that express either wild-type or a CMT2C causing TRPV4 mutant ($TRPV4^{R269C}$) to assess the effect of $TRPV4^{R269C}$ on neuron function *in vivo.* Selective expression of $TRPV4^{R269C}$ in *Drosophila* CCAP neurons (N_{CCAP}) results in a failure of *Drosophila* wing expansion that is blocked by genetically inactivating the channel pore, demonstrating the requirement of channel function in mediating this phenotype. Perforated patch clamp analysis of N_{CCAP} reveals that $TRPV4^{R269C}$ causes a calcium-dependent increase in N_{CCAP} neuronal excitability. This hyperexcitability is restored to control levels by application of a TRPV4 selective antagonist. High level expression of $TRPV4^{R269C}$ causes synaptic and dendritic degeneration, both of which are rescued genetically by inactivating the channel pore or pharmacologically by feeding larvae a TRPV4 selective antagonist. We conducted a genetic screen in N_{CCAP} and found that CaMKII knockdown potently suppresses the $TRPV4^{R269C}$ mediated wing expansion phenotype and selectively rescues degeneration of synapses but not dendrites. We also find that $TRPV4^{R269C}$, but not controls, disrupts mitochondrial transport in axons by increasing the number of stationary mitochondria. Our data demonstrate that $TRPV4^{R269C}$ elevates neuronal intracellular calcium which disrupts mitochondrial transport and mediates neurodegeneration through compartment-specific calcium-mediated signaling pathways, and supports the further investigation of TRPV4 antagonists as potential therapeutics for the treatment of CMT2C.

STRESS-INDUCED MECHANICAL ALLODYNIA, BLADDER HYPERSENSITIVITY, AND ANHEDONIA IN AN ANXIETY-PRONE MOUSE STRAIN

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Mood disorders, including anxiety and depression, are commonly observed among chronic pain patients with prevalence estimates ranging from 3 to 35%. Comorbidity between mood and chronic pain disorders has been linked to altered limbic regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Stress activates the HPA axis and can initiate and/or exacerbate symptoms related to both chronic pain and mood disorders. Previous studies from our laboratory have investigated the influence of early life stress on mechanical pain hypersensitivity, visceral hypersensitivity and behavioral evidence of mood disorder later in life. Here, we are testing the hypothesis that chronic stress exposure in adulthood can increase somatic and visceral sensitivity and anhedonic behaviors in a mouse strain with a genetic predisposition to anxiety. Adult, female A/J mice were exposed to repeated foot shock stress for 10 continuous days and tested for alterations in mechanical sensitivity, sucrose preference, visceromotor response (VMR) during urinary bladder distension, and serum corticosterone levels. Mice that underwent shock stress had a significantly decreased mechanical withdrawal threshold in the hind paw compared to their baseline and sham group measurements. Sucrose preference was measured prior to shock exposure and throughout the shock paradigm as an indicator of anhedonic behavior. Mice that underwent shock stress displayed a trend toward decreased sucrose preference, indicating anhedonia, in comparison to mice in the sham group that did not display anhedonia. Mice that underwent shock stress displayed significant increases in VMR during bladder distension compared to sham mice. Finally, serum corticosterone levels were significantly higher in the mice that underwent shock stress compared to sham mice, indicating a stress-induced increase in HPA axis output. Together these data suggest that chronic stress exposure can induce mechanical allodynia, visceral hypersensitivity, and depression-like behaviors in an anxiety-prone mouse strain. Future studies will incorporate gene expression in the hypothalamus, amygdala, and hippocampus, as well as investigation of possible downstream peripheral neuroimmune modulation and neuronal morphology changes.

ANALYSIS OF THE ADAPTABILITY OF GUILLAIN- BARRÉ SYNDROME BIOMARKERS IN JAPAN

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Guillain- Barré syndrome (GBS) is an acute monophasic immune-mediated neuropathy. As prognostic markers of GBS, modified Erasmus GBS outcome score (mEGOS), Erasmus GBS respiratory insufficiency score (EGRIS), and ΔIgG have been reported. However, the proportions of subtypes of GBS are known to be different between the western countries and Japan, it remains to be elucidated whether those markers can also be applied to GBS in Japan or not. We here investigated retrospectively 177 GBS patients and determined the mEGOS and the EGRIS of those cases. Among them, ΔIgG could be obtained in 79 cases. We evaluated the prognosis using GBS outcome score (Functional grade: FG) at 6 months; we called good prognosis when FG at 6 months was less than 3 and poor prognosis when that was 3 or more. As a result, in 25 cases with higher score than 6 at mEGOS on admission 8 cases (32%) had poor prognosis and in 32 cases with higher score than 9 at mEGOS at day 7 of admission 13 cases had poor prognosis. In 25 cases with higher score than 6 on EGRIS 14 cases (56%) needed the mechanical ventilator. Patients with good prognosis had higher ΔIgG(average: 1008mg/dl) than patients with poor prognosis(average:528mg/dl). We calculated the cut-off value of ΔIgG in 79 patients, which was 1108 mg/dl. 36 patients with higher ΔIgG than 1108 mg/dl could significantly walk independently at six months ($p<0.05$). 9 patients (21%) had poor prognosis in 43 patients with lower ΔIgG than 1108 mg/dl. 99 (60%) of 164 patients were treated with the single cycle of Intravenous immunoglobulin (IVIg). Other patients (40 %) were treated with the combined therapies, such as intra venous methylprednisolone and/or plasmapheresis or the second cycle of IVIg in addition to IVIg. Although there was no difference in prognosis between patients with the single cycle of Intravenous immunoglobulin (IVIg) and patients with the combined therapies, in the 24 patients who had FG>3 and mEGOS >6 on admission, the combined therapies made better prognosis than the single course of IVIg ($p<0.05$).
We found that mEGOS, EGRIS and ΔIgG were also available in Japan.
The efficacy of the combined therapies in severe GBS patients should be investigated in the future large scale prospective studies.

DEVELOPMENT OF BEST PRACTICE GUIDELINES FOR PAEDIATRIC CHARCOT-MARIE-TOOTH DISEASE

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Charcot-Marie-Tooth disease (CMT) often presents during childhood. Common symptoms include weakness, limb pain and cramps, foot deformity, and balance impairment. Guidelines for the optimal management of common problems experienced by children with CMT do not currently exist. Development of these guidelines will provide an evidence base for the management and monitoring of children with CMT. A series of systematic literature reviews utilising the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach were conducted to answer pre-specified key clinical questions related to the management of paediatric CMT. These included treatment recommendations for symptoms such as weakness, pain, balance impairment, joint deformity, and impaired upper limb function, and anticipatory monitoring for associated complications such as hip dysplasia. This yielded minimal to no evidence for the pre-specified clinical questions, and evidence-based management recommendations could not be made. Consensus-based statements will therefore be formulated via a three-round Delphi process, to be conducted in 2017. The Delphi panel will consist of local and international medical and allied health professionals who have experience in the management of children with CMT.

PXT3003, A FIXED COMBINATION OF BACLOFEN, NALTREXONE AND SORBITOL, FOR THE TREATMENT OF CHARCOT-MARIE-TOOTH DISEASE TYPE 1A (CMT1A): STATUS OF A MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED, PIVOTAL PHASE III STUDY (PLEO-CMT)

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Efficacy of PXT3003 in the treatment of adult patients CMT1A (n=80) was shown in a multicenter, randomized, double-blind, placebo-controlled phase II study (Attarian et al. 2014). PXT3003 taken 2x/day, orally, for 12 consecutive months was well tolerated and safe. Significant improvement of disability was observed for the highest tested dose, thought indicative for an early, meaningful change in disease course (meta-analysis by Mandel et al., 2015). This formed the rationale to initiate a multicenter, randomized, double-blind, placebo-controlled pivotal phase III study (ClinicalTrials.gov: NCT02579759) of PXT3003 in mildly to moderately affected CMT1A patients in December 2015. The primary objective is to assess the efficacy of 2 doses of PXT3003 compared to placebo on disability as measured by the mean change from baseline Overall Neurology Limitations Scale (ONLS) score at month 12 and 15. Furthermore, efficacy on the proportion of

responders (i.e. improvement of ONLS), impairment (CMTNS-V2), functional tests (10-MWT, QMT, 9-HPT), electrophysiological parameters (CMAP, SNAP and NCV) and quality of life (EQ-5D, VAS) are secondary endpoints. Pursuant this study, patients will be eligible for a 9-month extension study, in which PXT3003 assigned patients will continue with the previously assigned dose, whereas placebo patients will be randomized to one of the two PXT3003 doses. The study is conducted in 30 investigational sites in 8 countries (EU, Canada and US). In December 2016 patient randomization was completed (n=323). The screen failure rate was 26%, as expected (437 patients were screened). The independent DSMB recommended to continue the study as planned following a safety analysis on the first 100 patients treated for >3 months. Preliminary baseline characteristics are based on 313 patients (data not cleaned). The study population had a mean age of 40.8±13.3 years (range 16-65; male 41.2%) of which 97.8% had a confirmed genetic diagnosis of CMT1A. The mean CMTNS-v2 was 13.9±3.09 and the mean motor nerve conduction of the ulnar nerve was 23.4±11.3 m/s. Ten patients withdrew from the study, 3 due to adverse events unrelated to study treatment. The last patient completing the study is expected in March 2018.

IN VIVO IMAGING OF EPIDERMAL NERVE FIBERS

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Assessment of epidermal nerve fiber density and its structure integrity is critical for the diagnosis and evaluating the effectiveness of potential therapies in small fiber neuropathies. Currently, skin biopsies, at multiple sites, are most commonly used to assess these diseases. These studies are expensive and time consuming due to cumbersome processing and quantification techniques and serial biopsies over time are often not feasible due to costs and patient acceptance. Moreover, vast majority of normative data for skin biopsies in humans are available only for few distal sites and a significant proportion of patients with small fiber neuropathies have focal or regional symptoms not involving the commonly biopsied sites in the leg. Live imaging could overcome these limitations and provide a noninvasive real time assessment of epidermal nerve fibers all over the body. We previously found that anti-ganglioside antibody (AGA) is an effective neuronal delivery vector for transport of various cargos, such as fluorescent dyes, to peripheral nerves. In the current proof of concept study, we examined whether non-invasive multiphoton microscopy can be used to probe/image the epidermal nerve fibers in living animals after systemic and/or local delivery of fluorescently conjugated AGA. We found that the individual nerve endings in skin and cornea are distinctly labeled, and visualized under two-photon microscope. The epidermal nerve fiber labelling by fluorescent-tagged AGA was further validated using transgenic mice selectively expressing yellow fluorescent protein in their nervous system. *In-vivo* multiphoton imaging provide a tool with potential for dynamic longitudinal evaluation of small fiber neuropathies, including nerve degeneration and regeneration, without tissue removal. Thus, the use of multiphoton microscopy in conjunction with fluorescently labeled AGA as neuronal vector can have many research and clinical applications, such as labeling and live visualization of epidermal nerve fibers to assess small sensory nerve fibers in health and disease.

DYSREGULATED LIPID METABOLISM IN THE ABSENCE OF PERIPHERAL MYELIN PROTEIN 22 (PMP22)

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The majority of hereditary neuropathies are due to abnormalities in peripheral myelin protein 22 (PMP22), whose genetic variants include increased expression (gene duplication), haploinsufficiency (gene deletion), or point mutations. Phenotypic heterogeneity in clinical presentation is common among hereditary neuropathy patients even within the same family, the cause of which has not been determined. To investigate the role of PMP22 in the pathogenesis of the neuropathies we have generated and characterized PMP22 null ($PMP22^{-/-}$) mice (Amici et al., 2006) whose peripheral nerves show alterations in lipid metabolism (Lee et al., 2014). To examine the molecular changes underlying these abnormalities we determined the expression of cholesterol synthesis (SREBP2 pathway), and cholesterol uptake, transport and efflux genes (LXR pathway). In affected nerves, we found the cholesterol synthesis pathway inhibited, while the LXR pathway, and particularly apoE and ABCA1, upregulated at the mRNA and protein levels. Since PMP22 is expressed at low levels in the liver, the central organ for the regulation of cholesterol in the body, we studied liver tissue form $PMP22^{-/-}$ mice. Liver from $PMP22^{-/-}$ mice showed significant hepatomegaly, clear features of microvesicular steatosis, as well as marked increase in LXR pathway genes and proteins (ABCA1 and apoE), as compared to WT. Ultrastructural studies identified lipid droplets and significantly enlarged mitochondria in the liver of male $PMP22^{-/-}$ mice, which is not due to mitochondria fusion, as the levels of MFN 1 and 2 remained similar to WT. As disturbed hepatic cholesterol homeostasis induces the activation of Kupffer and stellate cells, we determined the extent of inflammation in nerve and liver tissues from $PMP22^{-/-}$ mice with leukocyte (CD11b) and macrophage markers (CD68). In nerve sections, we detected an increase in the number of CD11b+ cells, which was confirmed by Western blots. In the liver of $PMP22^{-/-}$ mice we found a significant increase in CD68-reactive Kupffer cells and elevated levels of TNF-alpha. The severe dysregulation of cholesterol metabolism in nerve and liver, including neuro- and

hepatic inflammation in the absence of PMP22- suggest that dysregulated cholesterol metabolism and inflammation may act as a disease modifier in PMP22-dependent neuropathies.

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