Neuromuscular Disorders

Volume 28 Suppl. 2 October 2018

Cited in: Current Contents/Life Sciences, Elsevier BIOBASE/Current Awareness in Biological Sciences, Index Medicus, MEDLINE, Neuroscience Citation Index, Reference Update, Research Alert, Science Citation Index, SciSearch. Also covered in the abstract and citation database Scopus®. Full text available on ScienceDirect®

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0960-8966(201810)28:S2:1-H

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NEUROMUSCULAR DISORDERS

October 2018

Vol. 28 Suppl. 2, October 2018

28 (Suppl. 2) S49–S212
ISSN 0960-8966

Neuromuscular Disorders

23rd INTERNATIONAL CONGRESS OF THE WORLD MUSCLE SOCIETY
Mendoza, Argentina
2nd–6th October 2018

Editor-in-Chief

V Dubowitz *UK*

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WMS World Muscle Society

Official Journal of the World Muscle Society

Neuromuscular Disorders

Aims and Scope

This international, **multidisciplinary** journal covers all aspects of neuromuscular disorders in childhood and adult life (including the muscular dystrophies, spinal muscular atrophies, hereditary neuropathies, congenital myopathies, myasthenias, myotonic syndromes, metabolic myopathies and inflammatory myopathies).

The Editors welcome original articles from all areas of the field:

- **Clinical aspects,** such as new clinical entities, case studies of interest, treatment, management and rehabilitation (including biomechanics, orthotic design and surgery);
- **Basic scientific studies** of relevance to the clinical syndromes, including advances in the fields of molecular biology and genetics;
- Studies of **animal models** relevant to the human diseases.

The journal is aimed at a **wide range** of clinicians, pathologists, associated paramedical professionals and clinical and basic scientists with an interest in the study of neuromuscular disorders.

In addition to original **research papers**; the journal also publishes **reviews** and mini-reviews, preliminary short communications and book reviews, and has editorial, correspondence and news sections. **Reports** on workshops and meetings, taking the form of a digested or very comprehensive commentary, pointing out some of the particular highlights in relation to the contributions and giving some detail of the area covered, important contributions and a list of participants, are also welcome.

The journal is published **twelve times a year** and aims at rapid publication of high-quality papers of scientific merit and general interest to a wide readership. There is also a **fast track for rapid publication** of new material of outstanding scientific merit and importance.

Printed by Henry Ling Ltd, Dorchester, UK

NMD Gene Table is published:
– online at http://www.musclegenetable.fr
– last printed issue NMD 26/12. This print version is also freely available at http://www.journals.elsevierhealth.com/periodicals/nmd

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Volume 28 Suppl. 2 (2018)

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Publication information: *Neuromuscular Disorders* (ISSN 0960-8966). For 2018 Volume 28 (12 issues) is scheduled for publication. Subscription prices are available upon request from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (http://www.elsevier.com/locate/nmd). Further information is available on this journal and other Elsevier products through Elsevier's website (http://www.elsevier.com). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of dispatch.

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The Instructions to Authors can be found on the journal's website www.elsevier.com/locate/nmd.

USA mailing notice: *Neuromuscular Disorders* (ISSN 0960-8966) is published monthly by Elsevier, Radarweg 29, 1043 NX Amsterdam, the Netherlands. Periodicals postage paid at Jamaica, NY 11431 and additional mailing offices.

USA POSTMASTER: Send address changes to *Neuromuscular Disorders*, Elsevier Customer Service Department, 3251 Riverport Lane, Maryland Heights, MO 63043, USA.

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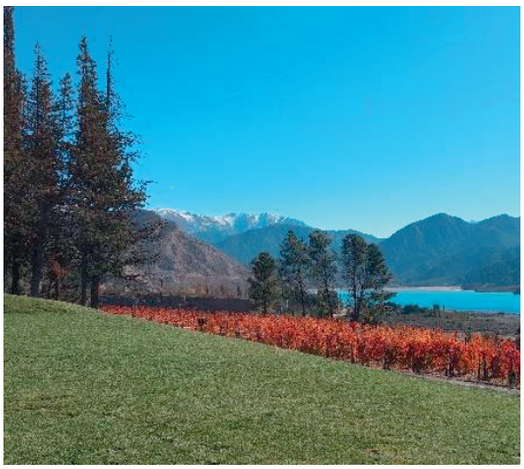
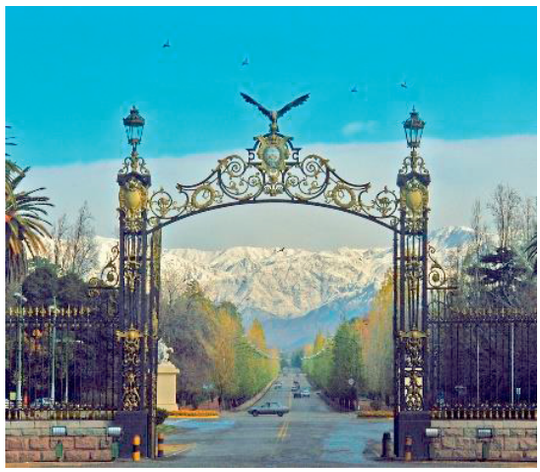


Neuromuscular Disorders

Editor-in-Chief
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PROGRAMME AND ABSTRACTS of the

23rd International Congress of the World Muscle Society

Mendoza, Argentina

2nd - 6th October 2018

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) S50–S51

www.elsevier.com/locate/nmd

Welcome to the World Muscle Society Congress in Mendoza

Dear Friends and Colleagues,

On behalf of the Local Organising Committee, we welcome you to the 23rd International Annual Congress of the World Muscle Society held for the first time in Argentina, in the beautiful city of Mendoza. This is the premier annual congress on neuromuscular disorders, attended by established and young physicians from a wide range of disciplines, basic and translational researchers, and physiotherapists from all over the world.

The capital of the province, Mendoza is situated in the northern-central part of the province and lies in a region of foothills and high plains, on the eastern side of the Andes mountains.

The Intercontinental Hotel is perfectly situated, within easy access to downtown Mendoza via East Access, only 15 minutes from the airport and on the route to the highly rated wine region. All rooms have a spectacular view of the mountains and the city.

The Convention Centre is well equipped for all the needs of our WMS congress and has two large auditoriums and ten smaller rooms for committee meetings and poster sessions - all of them on the same level on the first floor. The foyer on the ground and first floor is spacious and bright, ideal for catering and for networking with colleagues and friends.

You will have the opportunity to learn about the latest developments in world-wide myology during this 4-day international meeting from Wednesday 3rd October through to Saturday 6th October, with an opening reception on Tuesday 2nd October, and the traditional networking dinner on Friday evening.

We very much look forward to welcoming you to Mendoza!

Marcelo Rugiero

Message from the President of WMS

It is with great pleasure and the joy of anticipation that the neuromuscular scientific community of WMS will reunite in Mendoza in the spectacular setting between vineyards and the foothills of the Andes! Let me extend a warm welcome to all of you, clinicians, scientists, physiotherapists, and all the different disciplines engaged in furthering our knowledge and understanding of neuromuscular diseases for the benefit of patients!

We are without any doubt privileged to witness an important change of tides: never before have new and truly disease-course changing treatments burst onto the scene with a similar display of exciting results. This can be seen as the logical evolution of genetics and genomics profoundly transforming our approaches to understanding and informing our therapeutic endeavours. At the same time we are conscious that new therapeutic developments are inherently too slow for the patients who are waiting for them, and that many patients with neuromuscular diseases are still outside the current focus of treatment approaches using small molecules, biologics, antisense or gene therapy, let alone combinations thereof. So much more work is needed, and this is why our excitement about progress has to be kept in balance with critical appraisal and humbleness. There is so much more to learn!

Education, Enjoyment and Excitement has of course been the Leitmotif of the WMS 'Triple E Society' leading up to this 23rd Annual WMS Congress in Mendoza. **Marcelo Rugiero** and his local Organising Team have selected this beautiful venue for us and gone to great lengths to make sure there will be plenty of enjoyment both intellectually and through the wellbeing, which comes with meeting friends, being in a beautiful spot and receiving a great deal of attention. It is the second time that WMS comes to the South Americas after an unforgettable congress in 2005 in Iguassu Falls, Brazil, where we greeted Argentina through the mist of the spectacular waterfalls. So, finally, here we are to take this beautiful country in and learn more about its culture and ways of life. While it is certainly a long journey for many if not most, more than 600 delegates have followed the call and more than 400 abstracts have been received and will guarantee a rich palette of exciting new science,

https://doi.org/10.1016/j.nmd.2018.07.009
0960-8966

promote discussion and exchange, and hopefully incite new collaborations spanning the globe. This is our chance to contribute a mosaic stone to make this world a better place.

As every year WMS has received very generous support from **Elsevier**, the publishers of the WMS official journal, *Neuromuscular Disorders.* The annual royalties to the Society have risen again and are feeding into the WMS Education Fund, which in turn finances the 70 WMS Fellowships of €1000 for recipients worldwide (and €750 from within Argentina) to facilitate congress participation for young (under 40 years) clinicians and scientists in non-permanent positions, and also two Senior Fellowships for retired but still active long-standing WMS members. The Education Fund was further strengthened by a windfall from the successful 2017 WMS Congress in Saint Malo hosted by Gisèle Bonne.

We are also indebted to **Peter Bakker** from **Elsevier** for his continuous support, which includes the six Elsevier Prizes of €500 each for the best oral or poster presentations by young scientists as well as sponsoring the 20 additional Elsevier Awards for runners-up entitling them to a free one-year subscription to *Neuromuscular Disorders*. In addition WMS will award the President's Prize for the Young Myologist of the Year, funded from Victor Dubowitz' memoir "Ramblings of a Peripatetic Paediatrician", and an additional Prize for a Young First Time Presenter. Two further specialist Prizes will also be awarded: the Léa Rose Prize for the most important contribution to SMA research, generously endowed by violinist Natalia van der Mersch in memory of her late infant daughter Léa Rose; and the Duchenne Research Fund (UK) Prize for the best presentation by a young myologist on the therapy of Duchenne muscular dystrophy. All prizes will be awarded after careful evaluation by the WMS Prize Committee chaired by James Dowling.

WMS is fortunate to have again received substantial support from our **sponsors**, many of who are also present through symposia and stands as well as enriching the congress through scientific contributions. Industry involvement is crucial for developing successful therapies for patients. The field of neuromuscular disease therapies has experienced increasing investment and very prominent recent successes in key disease areas such as spinal muscular atrophy and Duchenne muscular dystrophy. May the exchange and discussions contribute to fertilize this development!

And, while we are enjoying Mendoza, we are also already looking forward to an exciting 2019 WMS Congress in Copenhagen, which will be organised by John Vissing and his local organising committee in the Tivoli, the famous amusement park in the centre of the city available on this occasion to WMS exclusively, promising a truly unique environment! You will find a flyer in your congress bag.

We are continuously trying to develop the congress format and content but also the way we create a space for exchange and how we select the venues. You can help us to do so by expressing your views, criticisms and appreciations in the appraisal forms. This congress is through you and for you – please let us know your opinion.

We hope that you will have a great time in Mendoza and enjoy the WMS spirit!

Thomas Voit
President, World Muscle Society

Congress Committee

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Marcelo Rugiero (Buenos Aires)
Werner Stenzel (Berlin)
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23rd WMS Congress – 2018 - Program (Summary)

Tuesday 2 October 2018

12:30-16:00	**WMS Executive Board Meeting** – Room: Lujan
14:00-18:00	**Registration opens - Setting up of posters**
16:00-18:00	**Afternoon refreshments**
18:00-18:45	**Opening Ceremony –** Auditorium
18:45-21:00	**Networking Reception**

Wednesday 3 October 2018

08:00	**Conference desk opens**
08:30-09:00	**Congress opening - Message from the President Thomas Voit** – Auditorium
09:00-10:30	**Neuromuscular junction defects** Invited lectures (I.1-2) *Chairpersons: Thomas Voit and Marcelo Rugiero*
10:30-11:00	**Morning refreshments, exhibition and posters –** Poster area
11:00-11:45	**Myasthenia gravis,** Invited lecture (I.3) - Auditorium *Chairpersons: Gisèle Bonne and Bruno Eymard*
11:45-13:15	**Selected oral presentations I - New genes, functions and biomarkers** (O.1-6) *Chairpersons: Gisèle Bonne and Bruno Eymard*
13:15-14:30	**Lunch, exhibition and posters**
13:30-14:30	**Sponsor Meeting** – Room: Perdriel
14:30-16:00	**Poster session 1: parallel sessions** (P.1-97) – Poster area Limb-girdle muscular dystrophy I (P.1-13) *Chairpersons: Bjarne Udd and Kevin Campbell* Duchenne muscular dystrophy - clinical (P.14-30) *Chairpersons: Alberto Dubrovsky and Jiri Vajsar* Duchenne muscular dystrophy - imaging and biomarkers (P.31-38) *Chairpersons: Lee Sweeney and Pierre Carlier* Congenital myopathies general and RYR1 (P.39-55) *Chairpersons: Jorge Bevilacqua and Edmar Zanoteli* Congenital myasthenic syndromes and myasthenia (P.56-75) *Chairpersons: Duygu Selcen and Ulrike Schara* SMA clincal data, outcome measures and registries (P.76-97) *Chairpersons: Laurent Servais and Eduardo Tizzano*
15:45-16:15	**Afternoon refreshments, exhibition and posters**

https://doi.org/10.1016/j.nmd.2018.06.016
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16:00-17:30 **Poster session 2: parallel sessions** (P.98-195) – Poster area
LGMD autosomal recessive and dominant (P.98-110)
Chairpersons: Isabelle Richard and Ivailo Tournev
DMD clinical therapies I (P.111-123)
Chairpersons: Francesco Muntoni and Nicolas Deconinck
DMD clinical therapies II (P.124-135)
Chairpersons: Ketan Patel and Ronald Cohn
Congenital myopathies (CNM) (P.136-148)
Chairpersons: Johann Böhm and Alan Beggs
Inflammatory myopathies (P.149-166)
Chairpersons: Ichizo Nishino and Werner Stenzel
SMA therapies I (P.167-182)
Chairpersons: Eugenio Mercuri and Arthur Burghes
Mitochondrial diseases (P.183-195)
Chairpersons: Anders Oldfors and Rahul Phadke

18:00-19:30 **Symposium 1**

Thursday 4 October 2018

07:00- **Conference desk opens**

07:30-09:00 **Symposium 2**

09:00-10:30 **Mitochondrial diseases I,** Invited lectures (I.4-5) – Auditorium
Chairpersons: Cornelia Kornblum and John Vissing

10:30-11:00 **Morning refreshments, exhibition and posters**

11:00-12:00 **Mitochondrial diseases II,** Invited lectures (I.6-7) - Auditorium
Chairpersons: Mariz Vainzof and Kevin Flanigan

12:00-13:30 **Selected oral presentations II - New insights into cellular functions** (O.7-12) – Auditorium
Chairpersons: Mariz Vainzof and Kevin Flanigan

13:30-14:00 **Lunch, exhibition and posters**

14:00-15:30 **Symposium 3**

15:30-18:00 **Poster viewing session** – Poster area

Friday 5 October 2018

07:00- **Conference desk opens**

07:30-08:30 **NMD Editorial Board Meeting** – Room: Agrelo

08:30-10:00 **New therapeutic approaches** Invited lectures (I.8-9) – Auditorium
Chairpersons: Nathalie Goemans and Benedikt Schoser

10:00-10:30 **Morning refreshments, exhibition and posters**

10:30-12:30 **Selected oral presentations III - New therapeutic approaches and their readout** (O.13-20) – Auditorium
Chairpersons: Nathalie Goemans and Benedikt Schoser

12:30-14:00 **Lunch, exhibition and posters**

14:00-15:30 **Symposium 4**

15:30-17:00 **Poster session 3: parallel sessions** (P.197-298) – Poster area
DMD treatment animal models (P.197-211)
Chairpersons: Thomas Crawford and Craig McDonald
Duchenne muscular dystrophy - genetics (P.212-224)
Chairpersons: Ieke Ginjaar and Alessandra Ferlini
Congenital myopathies: nemaline and titinopathies (P.225-244)
Chairpersons: Ana Lia Taratuto and Ana Ferreiro
Myofibrillar and distal myopathies (P.245-254)
Chairpersons: Montse Olivé and Hans-Hilmar Goebel
SMA therapies II and biomarkers (P.255-266)
Chairpersons: Susan Iannaccone and Richard Finkel
Metabolic myopathies I (P.267-277)
Chairpersons: Ros Quinlivan and Corrado Angelini
Registries and care of neuromusular disorders (P.278-298)
Chairpersons: Helen Roper and Tahseen Mozaffar

17:00-18:30 **Poster session 4: parallel sessions** (P.299-387) – Poster area
Duchenne muscular dystrophy - physiotherapy (P.299-322)
Chairpersons: Linda Lowes and Imelda de Groot
Congenital muscular dystrophies (P.323-334)
Chairpersons: Soledad Monges and Haluk Topaloğlu
CMT and neurogenic disease (P.335-347)
Chairpersons: Michael Shy and Peter Van den Bergh
Metabolic myopathies II (P.348-358)
Chairpersons: Antonio Toscano and Claudio Bruno
FSHD/OPMD/EDMD/DM1 (P.359-371)
Chairpersons: Julie Dumonceaux and Scott Harper
Next generation sequencing and experimental myology (P.372-387)
Chairpersons: Silvère van der Maarel and Conrad Weihl

20:00-00:00 **Networking dinner**

Saturday 6 October 2018

08:00- **Conference desk opens**

08:30-10:30 **Poster Highlights** – Auditorium
Chairpersons: Kathryn Swoboda and Werner Stenzel

10:00-10:30 **Morning refreshments, exhibition and posters**

10:30-11:30 **WMS General Assembly -** Auditorium

11:30-13:00 **Late breaking session -** Auditorium
Chairpersons: Valeria Ricotti and Carsten Bönnemann

13:00-13:30 **Prize giving and welcome to the 24th WMS Congress.**
Handover of the WMS flag and close of congress – Auditorium

13:30-14:30 **Lunch and end of congress**

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23rd WMS Congress – 2018 - Program

Tuesday 2 October 2018

12:30-16:00	**WMS Executive Board Meeting** – Room: Lujan
14:00-18:00	**Registration opens - Setting up of posters**
16:00-18:00	**Afternoon refreshments**
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Wednesday 3 October 2018

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08:30-09:00		**Congress opening - Message from the President Thomas Voit** – Auditorium
09:00-10:30		**Neuromuscular junction defects,** Invited lectures (I.1-2) *Chairpersons: Thomas Voit and Marcelo Rugiero*
	I.1	**Age-related neuromuscular junction instability: causes and consequences** M. Ruegg; P. Castets; S. Lin; H. Brenner; D. Ham; M. Rich
	I.2	**New genes and better treatment for congenital myasthenic syndromes** D. Beeson
10:30-11:00		**Morning refreshments, exhibition and posters**
11:00-11:45		**Myasthenia gravis;** Invited lecture (I.3) - Auditorium *Chairpersons: Gisèle Bonne and Bruno Eymard*
	I.3	**From trial-and-error to trials without errors in myasthenia gravis** J. Verschuuren
11:45-13:15		**Selected oral presentations I - New genes, functions and biomarkers** (O.1-6) *Chairpersons: Gisèle Bonne and Bruno Eymard*
	O.1	**Recessive mutations in *BET1* and *GOSR2* establish Q-SNARE Golgi-vesicle-transport genes as a cause for congenital muscular dystrophy with epilepsy** S. Donkervoort; Y. Hu; P. Shieh; J. Koliwer; L. Tsai; B. Cummings; M. Snyder; K. Chao; R. Kaur; D. Bharucha-Goebel; S. Iannaccone; D. MacArthur; A. Foley; M. Schwake; C. Bönnemann
	O.2	**Mutations in fast skeletal troponin C (*TNNC2*) cause contractile dysfunction** M. van de Locht; J. Winter; S. Conijn; W. Ma; M. Helmes; T. Irving; S. Donkervoort; P. Mohassel; L. Medne; C. Quinn; O. Neto; S. Moore; A. Foley; N. Voermans; C. Bönnemann; C. Ottenheijm
	O.3	**A patient-derived iPSC model reveals that genotoxic stresses can be risk factors by increasing the causative DUX4 expression in facioscapulohumeral muscular dystrophy (FSHD)** M. Sasaki-Honda; T. Jonouchi; M. Arai; A. Hotta; S. Mitsuhashi; I. Nishino; R. Matsuda; H. Sakurai
	O.4	**Single-cell RNA-sequencing in facioscapulohumeral muscular dystrophy disease etiology and development** A. van den Heuvel; A. Mahfouz; S. Kloet; J. Balog; B. van Engelen; R. Tawil; S. Tapscott; S. van der Maarel
	O.5	**Association of phosphorylated neurofilament heavy chain (pNF-H) with nusinersen treatment of SMA: analyses from the ENDEAR and CHERISH studies** B. Darras; R. Finkel; E. Mercuri; C. Sumner; M. Oskoui; E. Tizzano; M. Ryan; G. Zhao; M. Petrillo; C. Stebbins; W. Farwell
	O.6	**Free $Mg2^{+}$ intramuscular concentration determined by combined 31P and 1H NMR spectroscopy as a potential outcome measure in Duchenne muscular dystrophy** H. Reyngoudt; P. Carlier

https://doi.org/10.1016/j.nmd.2018.06.017
0960-8966

13:15-14:30 **Lunch, exhibition and posters**

Sponsor Meeting – Room: Perdriel

14:30-16:00 **Poster session 1: parallel sessions (P.1-97)** – Poster area

Limb-girdle muscular dystrophy I (P.1-13)
Chairpersons: Bjarne Udd and Kevin Campbell

P.1 **Limb-girdle muscular dystrophy type 2L: clinical, neurophysiological, and imaging correlation in the first reported Brazilian cases**
A. Coimbra Neto; T. Leoni; T. Rosa; C. Iwabe-marchese; A. Martinez; A. Nucci; M. Franca Junior

P.2 **ANO5 - Three different phenotypes and a new histological pattern**
L. Gonzalez-Quereda; G. Garrabou; M. Rodriguez; P. Gallano; A. Sanchez; J. Grau; J. Milisenda

P.3 **Phenotypic spectrum and muscle pathology in a Chinese cohort with *ANO5* recessive mutations**
S. Luo; S. Cai; M. Gao; J. Xi; Z. Liu; D. Yue; J. Lu; C. Zhao

P.4 **Axial muscular affection in patients with LGMD2L**
T. Khawajazada; J. de Stricker Borch; K. Rudolf; J. Dahlqvist; J. Vissing

P.5 **Effect of MAPK Inhibition on the differentiation of Rhabdomyosarcoma cell line TE671 combined with CRISPR/Cas9 technology: an *in vitro* model for the study of human muscle diseases**
N. De Luna; X. Suárez-Calvet; M. Garicano; E. Fernández-Simón; R. Rojas-Garcia; J. Diaz-Manera; L. Querol; I. Illa; E. Gallardo

P.6 **Functional recovery by readthrough therapy in a knock-in mouse model with nonsense dysferlin mutation**
J. Shin; K. Seo; J. Park; D. Kim

P.7 **Proteomic investigation of muscle-derived proteomic biomarkers of dysferlinopathy**
H. Park; Y. Choi

P.8 **Clinical outcome study for dysferlinopathy: three years of natural history data for clinical trial readiness**
M. James; A. Mayhew; R. Muni Lofra; M. Jacobs; A. Canal; T. Duong; R. Gee; M. Harman; S. Holsten; L. Lowes; E. Maron; B. Mendez; I. Pedrosa Belmonte; C. Sakamoto; C. Semplicini; C. Siener; S. Thiele; B. Vandervelde; K. Bushby; V. Straub

P.9 **A comparison of the utility between three muscle strength assessment methods in dysferlinopathy**
N. Miller; L. Lowes; M. James; L. Alfano; A. Mayhew; E. Maron; R. Gee; M. Harman; T. Duong; B. Vandervelde; C. Siener; S. Thiele; B. Mendez; A. Canal; C. Sakamoto; S. Holsten; I. Pedrosa Belmonte; C. Semplicini; V. Straub

P.10 **Imaging phenotype in dysferlinopathy and its relationship with disease duration and disability are unravelled by heatmaps and random forests**
D. Gómez-Andrés; J. Díaz; F. Munell; A. Sánchez-Montáñez; I. Pulido-Valdeolivas; L. Suazo; C. Garrido; J. Bevilacqua

P.11 **Clinical outcome study in dysferlinopathy: random forest approach to assess the relationship between baseline muscle MRI and longitudinal functional outcome measures**
J. Diaz-Manera; R. Fernández-Torron; M. James; A. Mayhew; M. Jacobs; S. Spuler; J. Day; K. Jones; D. Bharucha-Goebel; E. Salort-Campana; A. Pestronk; M. Walter; C. Paradas; T. Stojkovic; M. Mori-Yoshimura; E. Bravver; E. Pegoraro; J. Mendell; K. Bushby; V. Straub

P.12 **Clinical outcome study in dysferlinopathy: medical comorbidities and polytherapy in a large population of dysferlinopathy patients**
R. Fernandez-Torron; J. Diaz-Manera; M. James; A. Mayhew; S. Spuler; J. Day; K. Jones; D. Bharucha-Goebel; E. Salort-Campana; A. Pestronk; M. Walter; C. Paradas; T. Stojkovic; M. Mori-Yoshimura; E. Bravver; E. Pegoraro; J. Mendell; Jain Consortium; K. Bushby; V. Straub

P.13 **Rasch analysis of the individualised neuromuscular Quality of Life Questionnaire administered to patients with dysferlinopathy**
M. James; A. Mayhew; M. Jacobs; S. Spuler; J. Day; K. Jones; D. Bharucha-Goebel; E. Salort-Campana; A. Pestronk; M. Walter; C. Paradas; T. Stojkovic; M. Mori-Yoshimura; E. Bravver; J. Diaz Manera; E. Pegoraro; J. Mendell; K. Bushby; V. Straub

Duchenne muscular dystrophy - clinical (P.14-30)
Chairpersons: Alberto Dubrovsky and Jiri Vajsar

P.14 **The profile of Duchenne muscular dystrophy patients younger than 10 years old from KUKAS registry, Turkey**
A. Karaduman; I. Alemdaroğlu Gürbüz; E. Acar Aslan; M. Güngör; N. Bulut; G. Aydin; Ö. Yilmaz; B. Talim; H. Topaloğlu

P.15 **First report of natural history and survival in patients with Duchenne muscular dystrophy in Zimbabwe: a retrospective cohort study**
P. Karachunski; J. Dalton; R. Paulson; K. Mitchell; Z. Mugugunyeki; R. Machaka; J. Pazorora

P.16 **Epidemiology, clinical and genetic features of Duchenne disease in Portugal: a multicentre retrospective study**
C. Garrido; F. Palavra; M. Cardoso; A. Sousa; R. Rocha; D. Alves; M. Santos; M. Vila Real; J. Vieira; T. Coelho; I. Fineza; T. Moreno; M. Santos

P.17 **Reasons for first visit to neurologists in Chinese patients with dystrophinopathy: a survey study**
L. Wang; M. Xu; H. Li; C. Zhang

P.18 **The importance of nutrition in Duchenne muscular dystrophy**
I. Verhaart; M, Fiorotto; A. De Luca; S. Wong; R. Quinlivian; Z. Davidson; L. van den Engel-Hoek; M. van Putten; N. de Roos; K. Kinnett; C. Saure; O. Dorchies; I. Roberts; M. Franken-Verbeek; F. De Angelis; N. Goemans; P. Furlong; J. Kuijer; A. Aartsma-Rus; E. Vroom

P.19 **Prevalence of metabolic disorders in patients with Duchenne muscular dystrophy**
C. Saure; F. De Castro Perez; S. Monges; C. Caminiti

P.20 **Cognitive performance in Duchenne muscular dystrophy**
M. Miranda; A. Yaeko; C. Sá; L. Grossklauss; F. Favero; M. Voos

P.21 **Changes over years in the verbal IQ of patients with Duchenne muscular dystrophy**
H. Arahata; A. Miyoshi; A. Watanabe; Y. Kawano; A. Yamamoto; N. Sasagasako

P.22 **Evaluation of methylphenidate in males with Duchenne muscular dystrophy and a comorbid attention deficit hyperactivity disorder: a preliminary study**
D. Hellebrekers; J. Lionarons; S. Klinkenberg; C. Faber; J. Hendriksen; J. Vles

P.23 **Longitudinal follow-up of verbal working memory and processing speed in males with Duchenne muscular dystrophy**
D. Hellebrekers; N. Doorenweerd; D. Sweere; S. Kuijk; A. Aartsma-Rus; S. Klinkenberg; J. Vles; J. Hendriksen

P.24 **Cognition and cerebral structural abnormalities in dystrophinopathies**
P. Tavares; G. Conte; S. Passos; T. Rezende; L. Souza; T. Rosa; S. Ciasca; A. Nucci; M. França Jr

P.25 **Circadian rhythms in young boys with Duchenne muscular dystrophy**
R. Bendixen; A. Kelleher; N. Little; M. Feltman

P.27 **Descriptive characteristics of males with Duchenne muscular dystrophy using insurance claims data**
J. Karafilidis; O. Mayer; B. Griffin; K. Higgins

P.28 **The adult DMD patient. new challenges for an emerging phenotype**
A. Jáuregui; L. Mesa; J. Corderí; F. Chloca; D. Flores; A. Dubrovsky

P.29 **Analysis of respiratory function of Duchenne muscular dystrophy with Chilaiditi syndrome**
M. Ogasawara; A. Ishiyama; E. Takeshita; Y. Shimizu-Motohashi; H. Komaki; M. Sasaki

P.30 **Guidance regarding use of implantable cardioverter-defibrillators in Duchenne and Becker muscular dystrophy**
N. Kertesz; A. Kamp; W. Thompson; A. Barth; I. Law; S. Batlivala; N. Hanlon; A. Fournier; C. Spurney; M. Mori-Yoshimura; L. Markham; L. Cripe

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Chairpersons: Lee Sweeney and Pierre Carlier

P.31 **Serum creatinine: a promising biomarker for distinguishing Duchenne muscular dystrophy from Becker muscular dystrophy in patients aged ≤ 3 Years**
L. Wang; M. Chen; R. He; Y. Sun; J. Yang; L. Xiao; J. Cao; H. Zhang; C. Zhang

P.32 **Chemokine CXCL12 and osteopontin are highly expressed in Duchenne muscular dystrophy patients**
Y. Maeda; M. Ishizaki; Y. Nakajyo; Y. Yonemochi; T. Ueyama

P.33 **Skeletal muscle T1 mapping correlates with MFM scores in dystrophinopathies**
L. Souza; P. Tavares; S. Passos; C. Iwabe-Marchese; T. Rosa; A. Nucci; M. França Jr; S. Dertkigil

P.34 **MR biomarkers in imaging DMD clinical trial network**
S. Forbes; R. Willcocks; W. Triplett; H. Arora; W. Rooney; D. Wang; M. Daniels; E. Finanger; R. Finkel; G. Tennekoon; H. Sweeney; G. Walter; K. Vandenborne

P.35 **Higher MRI muscle fat fraction at similar age is associated with earlier loss of ambulation in Duchenne muscular dystrophy**
K. Naarding; H. Reyngoudt; E. van Zwet; M. Hooijmans; B. Wong; C. Tian; I. Rybalsky; K. Shellenbarger; J. Le Louër; P. Carlier; H. Kan; E. Niks

P.36 **Early impact on disease identified for Ezutromid using magnetic resonance spectroscopy (MRS) in Duchenne muscular dystrophy**
A. Heatherington; F. Muntoni; K. Vandenborne; G. Layton; D. Roblin & Imaging DMD Consortium; Phase Out DMD Study Group

P.37 **Upper extremity quantitative muscle ultrasound is related to disease severity in boys with Duchenne muscular dystrophy**
W. Stuij; M. Jansen; I. de Groot

P.38 **Description of Becker muscular dystrophy cardiomyopathy natural history by cardiac magnetic resonance imaging from the first to third decades provides insight for cardiac surveillance**
T. Johnston; K. Hor; M. Mah; L. Cripe

Congenital myopathies, general and RYR1 (P.39-55)
Chairpersons: Jorge Bevilacqua and Edmar Zanoteli

P.39 **Congenital cytoplasmic body myopathy – a nosological clarification**
M. Schülke; W. Stenzel; M. Schwarz; H. Goebel

P.40 **The distinct clinical phenotype of *PIEZO2* loss of function**
D. Saade; M. Lee; D. Bharucha-Goebel; S. Donkervoort; S. Neuhaus; K. Alter; C. Zampieri; C. Stanley; J. Matsubara; A. Nickolls; A. Micheil Innes; J. Mah; C. Grosmann; A. Nascimento; J. Colomer; F. Munell; G. Haliloglu; A. Foley; A. Chesler; C. Bönnemann

P.41 **Dominant *TNNC2* mutations cause a distinct congenital myopathy with vocal cord paralysis, ophthalmoplegia and clinical improvement over time**
S. Donkervoort; P. Mohassel; N. Voermans; C. Quinn; M. van de Locht; J. de Winter; S. Conijn; M. Helmes; L. Medne; O. Lopes Abath Neto; S. Moore; C. Ottenheijm; A. Foley; C. Bönnemann

P.42 **Congenital hyporegenerative microcytic anemia of unknown origin with XMEA-like muscle pathology**
J. Reimann; C. Scholtes; K. Cremer; S. Schoenberger; W. Kunz

P.43 **Prevalence of cytoplasmic bodies in a large series of diagnostic paediatric muscle biopsies**
M. Aizpurua; F. Cepas; A. Sarkozy; A. Manzur; F. Muntoni; C. Sewry; R. Phadke

P.44 **Mutations in the myomaker gene causes Carey-Fineman-Ziter syndrome with muscle fiber hypertrophy**
C. Hedberg-Oldfors; C. Lindberg; A. Oldfors

P.45 **A new congenital myopathy with multiple structured cores**
E. Malfatti; X. Lornage; J. Böhm; G. Brochier; R. Carlier; J. Laporte; M. Fardeau; N. Romero

P.46 **Novel *ASCC1* mutations causing prenatal-onset muscle weakness with arthrogryposis and congenital bone fractures**
J. Böhm; E. Malfatti; E. Oates; K. Jones; N. Romero; J. Laporte

P.47 ***ASC1*-related myopathy is associated with defects in myoblast proliferation and muscle growth: defining the phenotypic spectrum and understanding the pathogenesis of an emerging congenital myopathy**
I. Duband-Goulet; F. Catervi; E. Cabet; L. Davignon; C. Genetti; T. Gidaro; A. Koparir; S. Coppen; E. Pierce-Hoffman; A. Beggs; L. Servais; A. Ferreiro

P.48 **Hypercontractile congenital muscle stiffness**
C. Camelo; A. Da Silva; U. Reed; C. Bönnemann; E. Zanoteli

P.49 **Redefining morphological spectrum of *RYR1* recessive myopathies**
M. Garibaldi; J. Rendu; J. Brocard; E. lacene; M. Beuvin; G. Brochier; C. Labasse; A. Madelaine; E. Malfatti; J. Bevilacqua; F. Lubieniecki; S. Monges; A. Taratuto; I. Marty; N. Romero

P.50 **Loss of FKBP12-RYR1 binding *ex vivo* is a post-translational modification consistently evident across diverse ryanodine receptor 1-related myopathies**
J. Todd; J. Witherspoon; A. Kushnir; S. Reiken; M. Razaqyar; M. Shelton; I. Chrismer; C. Grunseich; A. Mankodi; C. Bönnemann; K. Meilleur

P.51 **Familial variation in phenotype in *RYR1*-related myalgia-rhabdomyolysis syndrome**
N. Witting; T. Solheim; J. Dahlqvist; N. Poulsen; M. Duno; J. Vissing

P.52 **Core and cytoplasmic bodies in a patient with asymptomatic hyperCKemia caused by a *RYR1* p.Arg163Cys mutation**
L. Gonzalez-Quereda; A. Pellisé; N. Vidal; M. Rodriguez; P. Gallano; M. Olivé

P.53 **Clinical, genetic and pathological characterization of a wide paediatric cohort of patients with dominant and recessive *RYR1*-related myopathy**
M. Sa; M, DiStefano; R. Mein; R. Phadke; L. Feng; P. Munot; R. Quinlivan; A. Manzur; S. Robb; M. Main; C. Sewry; A. Sarkozy; F. Muntoni

P.54 **Forced and slow vital capacities in *RYR1*-RM**
I. Chrismer; J. Witherspoon; B. Drinkard; M. Stockman; M. Shelton; A. Kuo; C. Allen; J. Todd; M. Jain; M. Meilleur

P.55 **Historical perspective and proposal for a unified ryanodine receptor 1-related myopathies nomenclature**
T. Lawal; J. Todd; J. Witherspoon; C. Bönnemann; S. Hamilton; J. Dowling; K. Meilleur

Congenital myasthenic syndromes and myasthenia (P.56-75)
Chairpersons: Duygu Selcen and Ulrike Schara

P.56 **Clinical manifestation and associated co-morbidities in patients with juvenile-onset myasthenia gravis: a retrospective study**
P. Karachunski

P.57 **Clinical features in juvenile myasthenia gravis in an Argentinian cohort**
M. García Erro; E. Cavassa; J. Muntadas; M. Pauni; G. Vázquez

P.58 **Myasthenia gravis anti-MuSK (MuSK-MG): therapeutic experience in 27 patients**
M. Rugiero; V. Salutto; V. Alvarez; M. Bettini; N. Genco; C. Mazia

P.59 **Ocular vestibular evoked myogenic potentials in myasthenia gravis**
R. de Meel; K. Keene; M. Tannemaat; J. Verschuuren

P.60 **Respiratory dysfunction in childhood myasthenia**
J. Vajsar; H. Katzberg; H. Qashqari; N. Chrestian; I. Narang

P.61 **Pembrolizumab induced myasthenia gravis and necrotizing myopathy with severe respiratory failure**
M. Rugiero; M. Bettini; F. Silveira; F. Sosa Albacete; S. Christiansen

P.62 **A case of clinically apparent myasthenia gravis after resection of non-myasthenic thymic cyst**
S. Ho; J. So; D. Bae

P.63 **Myasthenia gravis like syndrome after botulinum toxin type A injections for calf reduction**
J. So; S. Ho; D. Bae

P.64 **Living with myasthenia gravis**
E. Louet; S. Misdrahi; C. Orblin Bedos; S. Birnbaum; JY. Hogrel; P. Portero; B. Clair; B. Eymard; S. Demeret; G. Bassez; S. Berrih-Aknin; A. Jobic; P. Aegerter; P. Thoumie; T. Sharshar; M. Gargiulo; MGEX Study group

P.65 **Muscular pathological features in Lambert-Eaton myasthenic syndrome**
Y. Zhang; R. Ban; H. Liu; C. Pu; Q. Shi

P.66 **Congenital myasthenic syndromes: how do clinicians face diagnostic complexity and long-term prognosis in 2018?**
B. Eymard; D. Sternberg; M. Mayer; T. Stojkovic; E. Fournier; S. Nicole; A. Behin; P. Laforêt; L. Servais; S. Bauché; B. Fontaine; D. Hantaï; M. Fardeau; N. Romero

P.67 **Congenital myasthenic syndromes due to impaired principal coupling pathway in the ε-subunit of muscle acetylcholine receptor**
X. Shen; D. Selcen; J. Brengman; S. Shen; H. Durmus; V. Preethish-Kumar; A. Yuceyar; S. Vengalil; A. Nalini; F. Deymeer; S. Sine; A. Engel

P.68 **The p. N88K mutation in the *RAPSN* gene in Brazilian patients with congenital myasthenic syndrome**
E. Estephan; A. Zambon; P. Marchiori; A. Silva; C. Moreno; U. Reed; A. Töpf; H. Lochmüller; E. Zanoteli

P.69 **New *AGRN* mutations in a patient with limb-girdle congenital myasthenic syndrome**
S. Coppens; G. Glibert; N. Deconinck

P.70 **New homozygous mutation in *DPAGT1* gene leading to LG-CMS with tubular aggregates**
T. Gidaro; L. Vandenbrande; E. Malfatti; C. Labasse; P. Carlier; N. Romero; L. Servais; J. Böhm

P.71 **Unexpected findings of congenital myasthenic syndromes by NGS testing using an extended gene panel on neuromuscular patients in Norway**
C. Jonsrud; P. Aden; G. Hansen; M. Mork; B. Nygård; T. Popperud; M. Rasmussen; N. Songstad; K. Ørstavik; T. Fagerheim

P.72 **Clinical features of congenital myasthenic syndrome due to mutations in *COL13A1***
P. Rodriguez Cruz; J. Palace; D. Beeson

P.73 **Characterization of an Indian congenital myasthenic syndrome cohort by whole exome sequencing**
S. Balaraju; A. Töpf; P. Veeramani; S. Vengalil; K. Polavarapu; S. Nashi; J. Kirschner; R. Horvath; N. Atchayaram; H. Lochmüller

P.74 **Five years of salbutamol treatment in a girl with congenital myasthenic syndrome caused by mutations in *COL13A1***
F. Munell; D. Gomez-Andrés; L. Costa Comellas; A. Macaya; M. Gratacós; M. Dusl; J. Senderek; H. Lochmüller

P.75 **Development of a home-based assessment tool for monitoring fluctuations in symptoms in the myasthenic population**
V. Selby; G. Ramdharry; M. Hanna; F. Muntoni

SMA clincal data, outcome measures and registries (P.76-97)
Chairpersons: Laurent Servais and Eduardo Tizzano

P.76 **A prospective functional assessment in type 2 spinal muscular atrophy in the Spanish population. Importance of the age on disease progression rate**
D. Natera - de Benito; A. Frongia; M. Alarcón; A. Borras; J. Armas; J. Exposito; L. Carrera; L. Martorell; D. Moya; N. Padros; S. Roca; M. Vigo; J. Medina; J. Colomer; C. Ortez; A. Nascimento

P.77 **Two year longitudinal data of the European prospective natural history study of patients with type 2 and 3 spinal muscular atrophy**
A. Chabanon; M. Annoussamy; A. Daron; Y. Péréon; C. Cances; C. Vuillerot; N. Goemans; J. Cuisset; V. Laugel; U. Schara; T. Gidaro; A. Seferian; L. Lowes; P. Carlier; JY. Hogrel; C. Czech; R. Hermosilla; O. Kwaja; L. Servais

P.78 **Clinical and molecular features of proximal spinal muscle atrophy in Portugal: a multicentre retrospective study**
M. Oliveira Santos; C. Falcão de Campos; C. Garrido; I. Conceição; F. Palavra; L. Negrão; J. Pedro Vieira; C. Mendonça; T. Coelho; I. Fineza; M. Santos; T. Moreno

P.79 **The relationship between function and muscle strength in the upper limb in a cohort of children with spinal muscular atrophy type II and III – a prospective study**
E. Milev; V. Selby; J. Reznik; R. Tillmann; M. Iodice; M. Scoto; JY. Hogrel; F. Muntoni

P.80 **Survival and ventilation among those with type I spinal muscular atrophy: results from the 2017 Cure SMA membership survey**
L. Belter; J. Jarecki; C. Jones; A. Paradis; M. Jhaveri; S. Reyna; K. Hobby

P.81 **Anthropometric and nutritional assessment in SMA type II and III**
C. Saure; F. de Castro Perez; S. Monges

P.82 **Vitamin D status among patients with spinal muscular atrophy**
M. Martínez-Jalile; A. Lozano-Arango; C. Diemer; B. Suárez; K. Alvarez; C. Castiglioni

P.83 **Longitudinal study of body composition and bone mass in spinal muscular atrophy type 2/3**
N. DiIorgi; E. Medone; G. Brigati; S. Notarnicola; C. Panicucci; C. Fiorillo; M. Pedemonte; C. Minetti; M. Maghnie; C. Bruno

P.84 **Clinical discordance in spinal muscular atrophy siblings: the exception or the rule?**
S. Monges; J. Mozzoni; M. Franchi; S. Medrano; L. Gravina; H. Aráoz; F. de Castro; V. Aguerre; L. Alías; L. Chertkoff; E. Tizzano; S. Bernal

P.85 **Cognitive performance of children with 5q-spinal muscular atrophy: a systematic review**
G. Polido; M. Miranda; N. Carvas Junior; F. Caromano; U. Reed; E. Zanoteli; M. Voos

P.86 **Cognitive assessment in spinal muscular atrophy type 1-2 using eye tracking system**
L. Paternoster; S. Baijot; G. Deliens; N. Goemans; L. Servais; N. Deconinck

P.87 **Use of the ACTIVE-mini for quantifying movement in infants with spinal muscular atrophy**
L. Nelson; L. Alfano; D. Chen; N. Miller; M. Dugan; S. Rust; E. Lin; S. Lin; S. Wang-Price; C. Swank; M. Thompson; L. Lowes

P.88 **Associations between NMR, electrophysiological, strength and function variables in SMA type 2 and 3**
JY. Hogrel; M. Annoussamy; A. Chabanon; A. Daron; Y. Péréon; C. Cances; C. Vuillerot; N. Goemans; J. Cuisset; V. Laugel; U. Schara; E. Gargaun; T. Gidaro; A. Seferian; S. Turk; R. Hermosilla; E. Fournier; P. Baudin; P. Carlier; L. Servais; Study Group

P.89 **More than just fun and games: ACTIVE workspace volume video game quantifies meaningful change in function in individuals with spinal muscular atrophy**
L. Alfano; N. Miller; M. Iammarino; M. Moore-Clingenpeel; S. Lowes; M. Dugan; M. Waldrop; K. Flanigan; G. Noritz; C. Tsao; S. Al Zaidy; J. Kissel; L. Lowes

P.90 **The shifting landscape of SMA: development of a new mild mouse model to better understand disease in aging**
M. Deguise; A. Beauvais; A. Tiernay; B. Paul; E. McFall; Y. De Repentigny; R. Kothary

P.91 **Muscle imaging and function in patients with spinal and bulbar muscular atrophy**
J. Dahlqvist; S. Oestergaard; N. Poulsen; J. Vissing

P.92 **Clinical and molecular characterization of non-5q spinal muscular atrophies**
S. Calligaris; A. Guzmán; A. Savransky; C. Buompadre; F. Lubieniecki; C. Tesi Rocha; D. Tiziano; V. Fano; E. Tizzano; P. Gravina; S. Monges

P.93 **Collaborative data collection by TREAT-NMD registries to support post-marketing surveillance in spinal muscular atrophy**
J. Bullivant; V. Hodgkinson-Brechenmacher; M. Rodrigues; Study Group; 2; V. Straub; H, Dawkins; C. Campbell; N. Goemans

P.94 **Cure SMA membership: findings from the 2018 membership survey**
L. Belter; C. Jones; A. Paradis; M. Jhaveri; S. Reyna; K. Hobby; J. Jarecki

P.95 **Economic burden of infant-onset (type 1) spinal muscular atrophy: a retrospective claims database analysis**
O. Dabbous; J. Seda; M. Droege; D. Sproule

P.96 **Number needed to treat in spinal muscular atrophy type 1 with AVXS-101 relative to nusinersen**
O. Dabbous; M. Cloutier; A. Guerin; I. Pivneva; E. Wu; M. Droege; D. Sproule

P.97 **Development of a decision-analytic model for the economic evaluation of newborn screening for spinal muscular atrophy**
T. Dangouloff; M. Hiligsmann; J. Caberg; F. Boemer; L. Servais

15:45-16:15 **Afternoon refreshments, exhibition and posters**

16:00-17:30 **Poster session 2: parallel sessions** (P.98-195) – Poster area

LGMD autosomal ressessive and dominant (P.98-110)
Chairpersons: Isabelle Richard and Ivailo Tournev

P.98 **AAV-mediated gene transfer of *FKRP* for therapy of LGMD2I**
E. Gicquel; S. Brown; I. Richard

P.99 **Limb-girdle muscular dystrophy 2Z in a Bulgarian family**
T. Chamova; A. Taneva; M. Gospodinova; D. Zlatareva; K. Johnson; A. Töpf; V. Straub; I. Tournev

P.100 ***BVES* loss-of-function mutations in limb-girdle muscular dystrophy 2X with cardiac conduction disorders**
I. Nelson; W. De Ridder; B. Asselbergh; B. De Paepe; M. Beuvin; R. Ben Yaou; A. Boland; J. Deleuze; T. Maisonobe; B. Eymard; J. De Bleecker; S. Symoens; R. Schindler; T. Brand; A. Töpf; K. Johnson; V. Straub; P. De Jonghe; J. Baets; G. Bonne

P.101 **Recurrent rhabdomyolysis and subtle proximal weakness in two female siblings diagnosed with alpha sarcoglycanopathy and a review of the literature**
H. Sampaio; M. Farrar; A. Al Safar

P.102 **Limb girdle muscular dystrophy type 2A: divergent features of mitochondrial deficiencies associated with novel calpain-3 mutations**
R. El-Khoury; R. Sawaya; M. Lamaa; M. Ahdab-Barmada

P.103 **A very early onset of calpainopathy (LGMD2A)**
R. Andrade; L. Lima; M. Melo; A. Miranda

P.104 **Coalition to Cure Calpain 3: a patient organization committed to treating and ultimately curing limb girdle muscular dystrophy type 2A**
J. Levy; J. Boslego; M. Wrubel; L. Wrubel; M. Spencer

P.105 **Recessive limb-girdle muscular dystrophies in a Brazilian tertiary hospital: epidemiological, clinical and genetic profile**
A. Coimbra Neto; T. Leoni; A. Martinez; A. Nucci; M. Franca Junior

P.106 **Limb girdle muscular dystrophy: steps toward a comprehensive patient reported outcome**
M. Hunter; A. Hatzipolakis; C. Heatwole; M. Wicklund; J. Statland; C. Weihl; N. Johnson

P.107 **Limb-girdle muscular dystrophy in Taiwan: a referral center experience**
W. Liang; C. Wang; X. Tian; W. Chen; T. Kan; I. Nishino; L. Wong; Y. Jong

P.108 **Functional characterization of *DNAJB6* J-domain mutations**
P. Jonson; J. Sarparanta; S. Kawan; H. Luque; M. Jokela; B. Udd

P.109 **Clinical presentation of a new transportinopathy phenotype in an Hungarian family LGMD D2**
C. Angelini; R. Marozzo; V. Pegoraro

P.110 **Limb girdle muscular dystrophy type 1G caused by p.D378N mutation in *HNRPDL* gene with distal muscle weakness in a Chinese family**
Y. Da; Y. Sun; H. Chen; Y. lu; L. Di; X. Wen

DMD clinical therapies I (P.111-123)
Chairpersons: Francesco Muntoni and Nicolas Deconinck

P.111 **Preservation of function over time as measured by North Star ambulatory assessment in boys with nonsense mutation Duchenne muscular dystrophy treated with ataluren**
C. McDonald; L. Wei; F. Jin; G. Elfring; P. Trifillis; M. Souza; J. McIntosh; S. Peltz; F. Muntoni

P.112 **STRIDE^{TM}: A patient registry study examining the use of ataluren (Translarna^{TM}) in patients with nonsense mutation muscular dystrophy (nmDMD)**
F. Muntoni; I. Desguerre; M. Guglieri; E. Mercuri; A. Nascimento Osorio; J. Kirschner; M. Tulinius; F. Buccello; A. Delage; G. Elfring; C. Werner; T. Schilling; P. Trifillis

P.113 **Long-term effect - four years - of ataluren in fourteen patients with nonsense mutation Duchenne muscular dystrophy**
C. Ortez; J. Medina; M. Vigo; O. Moya; N. Padros; D. Natera De Benito; L. Carrera; J. Colomer; I. Zschaeck; C. Jimenez - Mallebrera; L. Solé; M. Cubells; C. Jou; A. Nascimento

P.114 **Vamorolone as a replacement for corticosteroids in Duchenne muscular dystrophy: phase 2a results in 48 DMD boys**
K. Nagaraju; P. Clemens; J. Damsker; J. McCall; L. Mengle-Gaw; L. Conklin; E. Smith; D. Castro; J. Mah; C. McDonald; N. Kuntz; R. Finkel; M. Guglieri; M. Tulinius; Y. Nevo; M. Ryan; R. Webster; A. Smith; L. Morgenroth; E. Hoffman

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H. Ismail; O. Dorchies; E. Gayi; L. Neff; L. Scapozza

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F. Richard; K. Vandenborne; H. Sweeney; E. Finanger; G. Tennekoon; P. Shieh; R. Willcocks; G. Walter; W. Rooney; S. Forbes; W. Triplett; S. Yum; M. Mancini; J. MacDougall; A. Fretzen; P. Bista; A. Nichols; J. Donovan

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R. Finkel; C. McDonald; H. Sweeney; M. Mancini; J. MacDougall; J. Donovan

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T. Nakayama; S. Kuru; H. Komaki; S. Takeda

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H. Tasfaout; S. Buono; I. Prokic; J. Ross; C. Kretz; S. Guo; P. Koebel; B. Monia; M. Bitoun; J. Ochala; J. Laporte; B. Cowling

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A. Alonso-Jimenez; X. Suárez-Calvet; I. Castellví; E. Gallardo; J. Diaz-Manera

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P.168 **Treatment by nusinersen in spinal muscular atrophy type 1 patients older than 7 months - 14 months follow-up**
K. Aragon-Gawinska; A. Seferian; L. Vanden Brande; A. Daron; A. Ulinici; N. Deconinck; M. Annoussamy; C. Vuillerot; C. Cances; J. Ropars; M. Chouchane; Z. Balintova; S. Modrzejewska; I. Cuppen; I. Hughes; M. Illingworth; C. Marini-Bettolo; K. White; M. Scoto; T. Gidaro; L. Servais

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A. Tagiyev; N. Bulut; G. Aydin; I. Alemdaroğlu Gürbüz; N. Eroğlu; O. Yilmaz; G. Haliloğlu; A. Karaduman; H. Topaloğlu

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D. Castro; M. Farrar; R. Finkel; M. Tulinius; K. Krosschell; K. Saito; Y. Zhang; I. Bhan; W. Farwell; S. Reyna

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P.177 **AVXS-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1: event-free survival and achievement of developmental milestones**
J. Mendell; S. Al-Zaidy; R. Shell; W. Arnold; L. Rodino-Klapac; T. Prior; L. Lowes; L. Alfano; K. Berry; K. Church; J. Kissel; S. Nagendran; J. L'Italien; D. Sproule; C. Wells; A. Burghes; K. Foust; K. Meyer; S. Likhite; B. Kaspar

P.178 **AVXS-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1: improvement in respiratory and bulbar function reduces frequency and duration of hospitalizations compared to natural history**
R. Shell; S. Al-Zaidy; W. Arnold; L. Rodino-Klapac; T. Prior; K. Kotha; G. Paul; L. Lowes; L. Alfano; K. Berry; K. Church; J. Kissel; S. Nagendran; F. Ogrinc; D. Sproule; C. Wells; K. Meyer; S. Likhite; B. Kaspar; J. Mendell

P.179 **AVXS-101 trial experience: CHOP-INTEND effectively quantifies early, rapid, and sustained improvements that precede subsequent milestone achievement but is not sensitive to continued advances in motor function in infants with SMA type 1**
L. Lowes; L. Alfano; M. Iammarino; N. Miller; M. Menier; J. Cardenas; D. Sproule; S. Nagendran; S. Al-Zaidy; J. Mendell

P.180 **AVXS-101 phase 1 gene replacement therapy clinical trial in spinal muscular atrophy type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age**
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P.181 **AVXS-101 gene replacement therapy for spinal muscular atrophy type 1: pivotal study (STR1VE) update**
J. Day; D. Feltner; F. Ogrinc; T. Macek; C. Wells; L. Muehring; J. L'Italien; D. Sproule; S. Nagendran; B. Kaspar; J. Mendell

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Y. Zhao; C. Yan

P.184 **Hypercapnic respiratory failure is common presentation in A3243G-related mitochondrial myopathy**
Y. Zhao; C. Yan

P.185 ***MTTL* 3243A>G mutation in a patient with a pure mitochondrial myopathy mimicking a distal myopathy, a striking uncommon phenotype**
A. Berardo; R. Reisin; G. Tasca; B. Udd

P.186 **Muscle histopathology in infantile *DNM1L*-related mitochondrial epileptic encephalopathy is key for clinical diagnosis**
E. Bertini; D. Verrigni; D. Battaglia; A. Torraco; L. Figa Talamanca; R. Carrozzo; D. Diodato; A. D'Amico; L. Papetti; D. Ghezzi; A. Ardissone; C. Lamperti; A. Legati; P. Goffrini

P.187 **Mitochondrial disorders with polymerase gamma 1 (*POLG1*) mutations: a study from tertiary referral centre**
N. Gayathri; P. Bindu; P. Govindaraj; C. Shwetha; K. Chetan; S. Deepha; N. Madhu; A. Taly

P.188 **Novel *POLG* mutations and variable clinical phenotypes in 5 Chinese patients with mitochondrial diseases**
Z. Wang; X. Zhao; J. Liu; W. Zhang; Y. Yuan

P.189 **A novel case of *MSTO1* gene related congenital muscular dystrophy with cerebellar involvement**
D. Ardicli; I. Zaharieva; A. Sarkozy; R. Phadke; C. Deshpande; I. Bodi; A. Siddiqui; J. U-King-Im; H. Jungbluth; F. Muntoni

P.190 **Novel variant of *GOSR2* gene in a patient presenting with mitochondrial myopathy and epilepsy**
M. Arroyo; B. Wong; C. Fuller; E. Schorry; E. Ulm; C. Tian

P.191 **Single muscle fiber analysis of extraocular and skeletal muscles in a CPEO patient harboring a pathogenic point mutation in the *MT-TN* gene**
E. Schlapakow; V. Peeva; M. Jeub; B. Wabbels; G. Zsurka; W. Kunz; C. Kornblum

P.192 **Severe isolated mitochondrial myopathy in childhood**
M. Loos; H. Aráoz; F. Lubieniecki; A. Taratuto; R. Caraballo; L. Chertkoff; S. Monges

P.193 **Unexpected genetic diagnosis of mitochondrial disease in three consanguineous Turkish families**
A. Topf; Y. Oktay; S. Balaraju; E. Yılmaz; E. Sönmezler; A. Yaramis; S. Güngör; S. Laurie; S. Beltran; I. Gut; H. Lochmüller; S. Hiz; R. Horvath

P.194 **Deficiency of the iron-sulphur cluster assembly protein ISCU causes impaired biogenesis or stability of respiratory chain complex I, II and IV in muscle**
C. Thomsen; Y. Sunnerhagen; A. Oldfors

P.195 **A novel multiplex chromogenic immunoassay for evaluating mitochondrial respiratory chain complex I and complex IV defects in diagnostic muscle biopsies**
D. Chambers; A. Kumar; L. Feng; I. Hargreaves; A. Lam; A. Manzur; F. Muntoni; C. Sewry; J. Poulton; R. Phadke

18:00-19:30 **Symposium 1**

Thursday 4 October 2018

07:00- Conference desk opens

07:30-09:00 **Symposium 2**

09:00-10:30 **Mitochondrial diseases I;** Invited lectures (I.4-5) – Auditorium
Chairpersons: Cornelia Kornblum and John Vissing

I.4 **Skeletal muscle manifestations in mitochondrial disease**
P. Mishra

I.5 **Perturbed mitochondrial homeostasis in the pathogenesis of mitochondrial disorders**
M. Zeviani; A. Dogan; M. Sanchez; R. Cerutti; C. Beninca; C. Viscomi

10:30-11:00 **Morning refreshments, exhibition and posters**

11:00-12:00 **Mitochondrial diseases II;** Invited lectures (I.6-7) - Auditorium
Chairpersons: Mariz Vainzof and Kevin Flanigan

I.6 **Deoxynucleoside therapy for mitochondrial DNA depletion disorders**
M. Hirano; C. Lopez-Garcia; X. Rosales; K. Engelstad; J. Uddin; C. Dominguez; C. Paradas; R. Marti; C. Garone

I.7 **Development of genetic therapy for mtDNA diseases**
S. Bacman; C. Pereira; U. Zekonyte; T. Arguello; S. Williams; J. Stewart; D. Jantz; C. Moraes

12:00-13:30 **Selected oral presentations II - new insights into cellular functions** (O.7-12) – Auditorium
Chairpersons: Mariz Vainzof and Kevin Flanigan

O.7 **Mitochondrial dysfunction triggers a pro-survival adaptive response through distinct DNA methylation of nuclear genes**
L. Mayorga; B. Salassa; C. Garcia Samartino; M. Loos; H. Eiroa; P. Romano; M. Roque

O.8 ***SEPN1*-related myopathy is a systemic metabolic disease: selenoprotein N maintains endoplasmic reticulum-mitochondrial interaction and regulates mitochondrial bioenergetics**
A. Filipe; E. Varone; S. Arbogast; A. Chernorudskiy; D. Pozzer; R. Villar; C. Dill; S. Dudhal; S. Fumagalli; M. De Simoni; M. Giovarelli; C. De Palma; P. Pinton; C. Giorgi; E. Clementi; S. Missiroli; S. Boncompagni; E. Zito; A. Ferreiro

O.9 **Dysfunctional mitophagy: a potential therapeutic target in inclusion body myositis**
S. Brady; E. Wang; J. Carver; M. Hofer; D. Hilton; D. Hilton-Jones; C. Fratter; J. Poulton

O.10 **The nuclear-cytoskeleton connection and nuclear positioning during muscle formation**
P. Gimpel; W. Roman; Y. Lee; B. Burke; E. Gomes; B. Cadot

O.11 **Secretion of toxic exosomes by muscle cells of ALS patients**
I. Le Gall; O. Lucas; S. Roquevière; V. Mariot; J. Dumonceaux; G. Ouandaogo; G. TRANE study; F. Ratti; A. Mejat; A. Durieux; J. Gonzales De Aguilar; C. Martinat; S. Knoblach; C. Raoul; W. Duddy; P. Pradat; S. Duguez

O.12 **Eccentric contraction causes loss of microtubule lattice organization in mdx skeletal muscle expressing mini- or micro-dystrophin**
D. Nelson; A. Lindsay; D. Lowe; J. Ervasti

13:30-14:00 **Lunch, exhibition and posters**

14:00-15:30 **Symposium 3**

15:30-18:00 **Poster viewing session**– Poster area

Friday 5 October 2018

07:30- **Conference desk open**

07:30-08:30 **NMD Editorial Board Meeting** – Room: Agrelo

08:30-10:00 **New therapeutic approaches;** Invited lectures (I.8-9) – Auditorium
Chairpersons: Nathalie Goemans and Benedikt Schoser

I.8 **Emerging therapeutic approaches for facioscapulohumeral muscular dystrophy (FSHD)**
S.Q. Harper

I.9 **Treatment of Duchenne muscular dystrophy: current efforts, bottlenecks and future prospects.**
E. Mercuri

10:00-10:30 **Morning refreshments, exhibition and posters**

10:30-12:30 **Selected oral presentations III - New therapeutic approaches and their readout** (O.13-20) – Auditorium
Chairpersons: Nathalie Goemans and Benedikt Schoser

O.13 **Genome editing for Duchenne muscular dystrophy**
C. Gersbach; C. Nelson; J. Robinson-Hamm; J. Kwon; V. Gough; M. Gemberling

O.14 **A mutation-independent approach via transcriptional upregulation of a disease modifier gene rescues muscular dystrophy *in vivo***
D. Kemaladewi; P. Bassi; K. Lindsay; S. Erwood; E. Hyatt; K. Place; R. Marks; K. Gawlik; M. Durbeej; E. Ivakine; R. Cohn

O.15 **Humoral and cell mediated immune response to new dystrophin after morpholino-induced exon skipping therapy in dystrophin-deficient mdx mice**
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O.16 **Myostatin expression is a reliable and quantifiable biomarker to monitor dose-dependent drug response in muscular dystrophy**
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O.18 **Significantly reduced muscle damage and inflammation observed in Duchenne muscular dystrophy patients following ezutromid treatment**
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O.20 **Results from ATB200-02: first-in-human, open-label, phase 1/2 study of ATB200 co-administered with AT2221 for Pompe disease**
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P.293 **A novel, ultrafast and robust NMR imaging approach to evaluate disease activity and chronic degenerative changes in skeletal muscle using an optimal fingerprinting radial sequence**
B. Marty; P. Carlier

P.294 **Muscle biopsy in the study of muscle disease in pediatric population**
R. Escobar; R. Gejman; C. Jaque; M. Beytia; D. Avila; J. Casar; O. Trujillo; R. Fadic

P.295 **HyperCKemia asymptomatic or oligosymptomatic in an Argentinian neuropediatric cohort**
M. Garcia Erro; E. Cavassa; J. Muntadas; M. Pauni; G. Vazquez

P.296 **ICD code refinement for Duchenne/Becker muscular dystrophy**
A. Kennedy; R. Valdez; C. Westfield; J. Bolen; K. Kinnett; D. Perez; P. Furlong

P.297 **Treatment responsive outcome measures in mouse models of neuromuscular disease**
A. Mullen; K. Uaesoontrachoon; S. Srinivassane; M. Moraca; W. Ross; A. MacKinnon; C. Bell; E. Gillis; J. Rowsell; M. Malbasic; M. Barkhouse; J. Warford; D. Shala; E. Hoffman; K. Nagaraju

P.298 **Development of a microRNA-155 inhibitor as a therapeutic for neuroinflammatory and neurodegenerative diseases**
D. Escolar; M. Hermreck; H. Semus; D. Hood; A. Jackson

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Duchenne muscular dystrophy - physiotherapy (P.299-322)
Chairpersons: Linda Lowes and Imelda de Groot

P.299 **Minimal detectable change in the North Star ambulatory assessment (NSAA) in Duchenne muscular dystrophy (DMD)**
F. Muntoni; A. Manzur; A. Mayhew; NorthStar Clinical Network; J. Signorovitch; G. Sajeev; Z. Yao; I. Dieye; M. Jenkins; S. Ward

P.300 **Prognostic factors for changes in 4-stair climb ability in patients with Duchenne muscular dystrophy**
N. Goemans; B. Wong; J. Signorovitch; G. Sajeev; M. Jenkins; I. Dieye; Z. Yao; I. Hossain; S. Ward

P.301 **Home based movement monitoring allows pivotal trials in DMD with ten times less patients than classical outcomes measures**
L. Servais; E. Gasnier; M. Grelet; T. Gidaro; A. Seferian; D. Vissieres

P.302 **Genetic association study of articular range of motion in the CINRG Duchenne natural history study**
T. Duong; L. Bello; E. Henricson; E. Hoffman; C. McDonald; H. Gordish-Dressman; CINRG Investigators

P.303 **Development of a conversion method to enable an accurate PUL v.2 score from PUL v.1.2 data in a cohort of Duchenne muscular dystrophy patients**
V. Selby; V. Ricotti; A. Mayhew; D. Ridout; J. Pitchforth; E. Niks; L. Servais; I. de Groot; V. Straub; E. Mercuri; F. Muntoni

P.304 **Relationship of lower extremity strength and range of motion on timed function tests in Duchenne muscular dystrophy**
T. Duong; H. Gordish-Dressman; M. Pavlvolgyi; M. Fensterwald; C. McDonald; E. Henricson; CINRG Investigators

P.305 **Disease progression in arm *versus* leg muscles in Duchenne muscular dystrophy**
H. Arora; R. Willcocks; S. Forbes; W. Triplett; W. Rooney; D. Wang; M. Daniels; E. Finanger; G. Tennekoon; J. Brandsema; H. Sweeney; G. Walter; K. Vandenborne

P.306 **Utility of the Bayley-III, North Star Ambulatory Assessment, and 100-meter timed test in quantifying gross motor delay in very young boys with Duchenne muscular dystrophy**
N. Miller; L. Alfano; M. Iammarino; M. Dugan; M. Moore-Clingenpeel; S. Al-Zaidy; C. Tsao; M. Waldrop; K. Flanigan; J. Mendell; L. Lowes

P.307 **Relationships between hand strength and function in non-ambulant patients with Duchenne muscular dystrophy or spinal muscular atrophy**
V. Decostre; M. Anoussamy; M. De Antonio; A. Canal; L. Servais; JY. Hogrel

P.308 **Determination of the minimal clinically important difference (MCID) for clinical trial outcome measures in Duchenne muscular dystrophy**
J. Pitchforth; J. Domingos; M. Iodice; A. Mayhew; F. Muntoni

P.309 **The effects of trunk and lower extremity flexibility on lumbar lordosis in children with Duchenne muscular dystrophy**
L. Akkurt; G. Aydin; I. Alemdaroğlu Gürbüz; A. Karaduman; H. Topaloğlu; Ö. Yilmaz

P.310 **The comparison of children with Duchenne muscular dystrophy and healthy peers in terms of pulmonary and upper extremity functions**
N. Bulut; G. Aydin; i. Alemdaroglu Gürbüz; A. Karaduman; H. Topaloğlu; O. Yilmaz

P.311 **The effect of kinesiologic taping on balance in Duchenne muscular dystrophy**
G. Aydin; I. Alemdaroğlu Gürbüz; N. Bulut; A. Karaduman; H. Topaloğlu; O. Yilmaz

P.312 **Factors influencing spontaneous maximal stride speed in individual Duchenne muscular dystrophy boys**
C. Lilien; M. Grelet; E. Gasnier; T. Gidaro; A. Seferian; A. Rigaud; D. Vissière; L. Servais

P.313 **Use of a powered arm support devices for upper limb function in non-ambulatory men with Duchenne muscular dystrophy**
R. Bendixen; A. Kelleher; M. Feltman; N. Little

P.314 **Kinematic/behavioural fingerprints in Duchenne muscular dystrophy and their clinical applications**
V. Ricotti; S. Haar; V. Selby; T. Voit; A. Faisal

P.315 **Stride to height ratio as a new ambulatory outcome measure in Duchenne muscular dystrophy**
E. Henricson; R. Abresch; A. Bagley; E. Goude; C. Owens; L. Williams; C. McDonald

P.316 **Utility of ACTIVE workspace volume as a clinically meaningful measure of functional capacity in individuals with neuromuscular disease**
M. Iammarino; L. Alfano; N. Miller; M. Dugan; M. Moore-Clingenpeel; S. Al-Zaidy; C. Tsao; M. Waldrop; K. Flanigan; L. Rodino-Klapac; J. Mendell; L. Lowes

P.317 **Clinically meaningful change on the 100-meter timed test in neuromuscular diseases**
L. Alfano; N. Miller; M. Iammarino; K. Berry; M. Moore-Clingenpeel; M. Dugan; S. Al-Zaidy; C. Tsao; L. Rodino-Klapac; M. Waldrop; K. Flanigan; J. Mendell; L. Lowes

P.318 **Insights from a multisite study utilizing dedicated technology to assess electrical impedance myography as an outcome measure for Duchenne muscular dystrophy**
C. Zaidman; K. Kapur; B. Darras; B. Wong; M. Yang; M. Leitner; L. Dalle Pazze; M. Buck; L. Freedman; S. Rutkove

P.319 **Can we use elastic bandage in children with Duchenne muscular dystrophy by therapy taping methods? Pilot study**
C. Iwabe-Marchese; N. Morini Jr; c. Sanches; T. Rosa

P.320 **Trunk movement and muscle activity in children with Duchenne muscular dystrophy when performing daily activities**
L. Peeters; I. Kingma; J. van Dieën; I. de Groot

P.321 **Bringing the spoon to the mouth or the mouth to the spoon? The analysis of compensatory movements of simulated feeding in Duchenne muscular dystrophy: a case-control study**
M. Artilheiro; E. Oliveira; N. Carvas Junior; F. Favero; F. Caromano; C. Sá; M. Voos

P.322 **Development of dynamic trunk and head supportive devices for children with neuromuscular disorders**
L. Peeters; M. Mahmood; S. Verros; H. Koopman; I. de Groot; Symbionics working group

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M. Shichiji; K. Ishigaki; T. Sato; A. Yamashita; S. Nagata

P.324 **Clinical characteristics and long-term course of selenoprotein N1 related myopathy in a large multi-centric cohort**
A. Silwal; M. Scoto; D. Ridout; A. Schmidt; A. Laverty; M. Henriques; L. D'Argenzio; M. Main; R. Mein; A. Sarkozy; A. Manzur; F. Al-Ghamdi; C. Genetti; F. Abel; G. Haliloglu; D. Ardicli; H. Topaloğlu; A. Beggs; F. Muntoni

P.325 **Severe loss of semimembranosus muscle bulk is an early phenomenon in SEPN1-related muscle disorders: toward early recognition of early-onset muscle disorders by imaging**
F. Munell; D. Gomez-Andres; A. Sanchez-Montañez; L. Costa Comellas; S. Ferrer-Aparicio; P. Romero; S. Quijano-Roy; M. Olivé

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L. Le Goff; M. Fink; G. Norato; P. Rippert; K. Meilleur; R. Foley; M. Jain; M. Waite; S. Donkervoort; C. Bönnemann; C. Vuillerot

P.327 **A model for dominant-mutated collagen VI-related disorder and allele-specific gene silencing therapy**
S. Noguchi; M. Ogawa; I. Nishino

P.328 **Pneumothorax in Ullrich congenital muscular dystrophy**
Y. Arahata; A. Ishiyama; M. Ogawa; S. Noguchi; R. Tanaka; E. Takeshita; Y. Shimizu-Motohashi; H. Komaki; Y. Saito; I. Nishino

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A. Foley; M. Leach; G. Averion; Y. Hu; P. Yun; S. Neuhaus; D. Saade; C. Arevalo; M. Fink; J. DeCoster; C. Mendoza; O. Mayer; R. Hausmann; D. Petraki; K. Cheung; C. Bönnemann

P.330 **Long-term motor function in collagen VI-related myopathies is associated with the maximal motor ability achieved: a classification proposal**
D. Natera - de Benito; R. Foley; J. Diaz-Manera; M. Fink; A. Mebrahtu; J. Minal; S. Donkervoort; Y. Hu; D. Cuadras; L. Carrera-Garcia; M. Alarcón; J. Milisenda; R. Dominguez; M. Olive; C. Jou; J. Colomer; C. Jimenez-Mallebrera; C. Bönnemann; A. Nascimento

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M. Jain; K. Meilleur; G. Norato; M. Waite; M. Leach; S. Donkervoort; A. Foley; C. Bönnemann

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K. Gawlik; V. Harandi; R. Cheong; A. Petersen; M. Durbeej

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E. Bugiardini; R. Phadke; R. Maas; A. Pittman; B. Kusters; J. Morrow; M. Parton; A. Nunes; M. Akhtar; P. Syrris; L. Lopes; T. Fotelonga; H. Houlden; P. Elliott; M. Hanna; J. Raaphorst; D. Burkin; E. Matthews

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P. Massaro Sanchez; A. Savransky; C. Rugilo; S. Monges

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D. Saade; D. Bharucha-Goebel; G. Norato; A. Foley; M. Waite; M. Jain; S. Debs; R. Vasavada; C. Nichols; R. Kaur; S. Donkervoort; S. Neuhaus; Y. Hu; T. Lehky; S. Gray; M. Fink

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E. Estephan; P. Sampaio; F. Souza; M. Rocha; E. Zanoteli; W. Marques Jr

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P.343 **Colchicine induced neuromyopathy in a patient using concomitant diuretics**
S. Ho; D. Bae

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O. Ekmekci; M. Argin; H. Karasoy

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R. Al-dahhak; J. Conway; L. Bostan-Shirin

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S. Cao; S. Parelkar; H. Ko; P. Thompson; L. Hayward

P.347 **Feasibility and validation of modified oculobulbar facial erspiratory score (mOBFRS) in amyotrophic lateral sclerosis**
N. Goyal; M. Wencel; N. Araujo; E. Medina; D. Nguyen; L. Zhang; T. Mozaffar

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K. Ogata; M. Kosuga; E. Takeshita; T. Matsumura; K. Ishigaki; S. Ozasa; H. Arahata; K. Sugie; T. Takahashi; S. Kuru; M. Kobayashi; H. Takada; A. Hattori; M. Takahashi; N. Tanaka; T. Kimura; M. Funato; T. Okuyama; H. Komaki

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S. Rico; B. Schoser; D. Dimmock; M. Lawlor; E. James; M. Morton; S. Prasad

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Y. Lun; S. Xu; R. Soska; A. Nair; M. Frascella; A. Garcia; A. Ponery; J. Feng; C. Della Valle; R. Gotschall; H. Do; K. Valenzano; R. Khanna

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S. Wenninger; E. Greckl; H. Babacic; B. Schoser

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H. Kölbel; A. Della Marina; O. Kaiser; F. Stehling; J. Weis; A. Abicht; U. Schara

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V. Decostre; P. Laforêt; K. Kachetel; A. Canal; G. Ollivier; F. Petit; P. Labrune; JY. Hogrel

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K. Visuttijai; C. Thomsen; C. Hedberg-Oldfors; A. Oldfors

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JY. Hogrel; C. Chéraud; I. Ledoux; G. Ollivier; R. Ben Yaou; F. Leturcq; A. Behin; T. Stojkovic; B. Eymard; P. Laforet

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P.360 **Longitudinal MR evaluation of inflammatory lesions in muscle of patients with facioscapulohumeral muscular dystrophy**
J. Dahlqvist; N. Poulsen; S. Oestergaard; F. Fornander; A. Eisum; C. Thomsen; J. Vissing

P.361 **Estimating thigh muscle volume using bioelectrical impedance analysis with reference to contractile muscle volume assessed by nuclear magnetic resonance imaging**
D. Bachasson; J. Mosso; B. Marty; P. Carlier; JY. Hogrel

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J. Eidahl; L. Zhang; M. Hoover; O. Branson; M. Freitas; S. Harper

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C. Giesige; L. Wallace; K. Heller; J. Eidahl; A. Fowler; N. Pyne; N. Saad; M. Alkharsan; A. Rashnonejad; G. Chermahini; J. Domire; D. Mukweyi; S. Garwick-Coppens; S. Guckes; K. McLaughlin; L. Rodino-Klapac; S. Harper

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N. Saad; M. Al-Kharsan; S. Garwick-Coppens; N. Pyne; S. Harper

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J. Statland; E. Bravver; C. Karam; L. Elman; N. Johnson; N. Joyce; J. Kissel; P. Shieh; L. Korngut; C. Weihl; R. Tawil; A. Amato; C. Campbell; A. Genge; G. Manousakis; A. Leneus; B. Miller; M. Sherman; C. Glasser; K. Attie

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V. Strings-Ufombah; A. Malerba; S. Harbaran; F. Roth; O. Cappellari; N. Nguyen; S. Kao; K. Takahashi; C. Kloth; P. Roelvink; G. Dickson; C. Trollet; D. Suhy

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A. Ishiyama; S. Kusabiraki; M. Inoue; Y. Oya; H. Miyahara; E. Takeshita; Y. Motohashi; H. Komaki; M. Sasaki; I. Nishino

P.369 **A Chinese case of the early onset recessive Emery-Dreifuss-like phenotype without cardiomyopathy**
L. Wang; H. Li; C. Zhang

P.370 **Diffusion tensor imaging and voxel based morphometry correlates with the CTG repeats and motor function in adult onset myotonic dystrophy type 1**
J, Park; S, Hwang; Y, Chang; H, Song

P.371 **Do scientific publications fit with DM1 individuals expectations? - A systematic review and comparative study**
M. De Antonio; C. Dogan; D. Hamroun; A. Geille; B. Eymard; Study Group; G. Bassez

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Chairpersons: Silvère van der Maarel and Conrad Weihl

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S. Donkervoort; A. Foley; D. Saade; S. Neuhaus; P. Mohassel; D. Bharucha-Goebel; K. Chao; B. Cummings; M. Lek; D. MacArthur; C. Bönnemann

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S. Luo; M. Xue; J. Sun; K. Qiao; J. Song; s. Cai; W. Zhu; L. Zhou; J. Xi; J. Lu; X. Ni; T. Dou; C. Zhao

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J. Lee; H. Shin; S. Lee; J. Choi; S. Kim; Y. Choi

P.376 **International DMD: a project devoted to dystrophin mutation identification by NGS technology in eastern Europe and northern African countries**
R. Selvativci; C. Trabanelli; S. Neri; R. Rossi; S. Fini; P. Rimessi; A. Venturoli; M. Neri; F. Gualandi; A. Ferlini

P.377 **The latin America experience with a next generation sequencing genetic panel for recessive limb-girdle muscular weakness**
T. Almeida; M. Guecaimburu Ehuletche; A. Perna; J. Bevilacqua; A. Dubrovsky; M. Franca; S. Vargas; M. Hegde; K. Claeys; V. Straub; N. Daba; R. Faria; A. Loaeza; V. Luccerini; M. Periquet; S. Sparks; N. Thibault; R. Araujo

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E. Zapata-Aldana; C. Campbell

P.379 **Transcriptome analysis of trans-differentiated myotubes for the diagnosis of neuromuscular disorders**
H. Gonorazky; S. Naumenko; D. Kao; P. Mashouri; A. Ramani; K. Mathews; M. Tarnopolsky; S. Moore; M. Brudno; J. Dowling

P.380 **The complexity of splicing pattern in human adult skeletal muscles: a key to understanding genotype-phenotype correlations**
M. Savarese; P. Jonson; S. Huovinen; L. Paulin; P. Auvinen; B. Udd; P. Hackman

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A. Ribeiro Junior; R. Ishiba; S. Alcântara Fernandes; C. Freitas Almeida; D. Ayub Gerrieri; A. Fernandes dos Santos; I. Santos; E Souza; M. Vainzof

P.382 **Klf5 has essential roles in myoblast differentiation and survival during fetal muscle development**
S. Hayashi; Y. Oishi; I. Manabe; I. Nishino

P.383 **Cullin-3 is required for normal skeletal muscle development**
J. Blondelle; K. Tallapaka; P. Shapiro; M. Ghassemian; J. Singer; S. Lange

P.384 **RNAseq in urine-derived stem cells identified the expression of 308 neuromuscular gene transcripts**
M. Falzarano; H. Osman; R. Rossi; R. Selvatici; M. Neri; F. Gualandi; M. Fang; l. Zhiyuan; A. Grilli; S. Bicciato; A. Ferlini

P.385 **Physician-Level muscle disease classifier for computer-aided diagnostics with neural networks**
Y. Kabeya; Y. Takeuchi; H. Nakano; M. Okubo; M. Inoue; R. Tokumasu; I. Ozawa; A. Takano; T. Iwamori; S. Yonezawa; I. Nishino

P.386 **A versatile, modular digital script for automated high-throughput multiparametric myofibre analysis in brightfield and epifluorescent paradigms**
M. Ellis; V. Sardone; S. Torelli; S. Saeed; A. Sigurta; N. Hill; D. Scaglioni; L. Feng; C. Sewry; M. Singer; F. Muntoni; R. Phadke

P.387 **Nonsense mutation induced exon skipping in Becker muscular dystrophy**
M. Okubo; S. Noguchi; S. Hayashi; M. Matsuo; I. Nishino

20:00-00:00 **Networking dinner**

Saturday 6 October 2018

08:00-	**Conference desk opens**
08:30-10:30	**Poster Highlights** – Auditorium *Chairpersons: Kathryn Swoboda and Werner Stenzel*
10:00-10:30	**Morning refreshments, exhibition and posters**
10:30-11:30	**WMS General Assembly -** Auditorium
11:30-13:00	**Late breaking session -** Auditorium *Chairpersons: Valeria Ricotti and Carsten Bönnemann*
13:00-13:30	**Prize giving and welcome to the 24th WMS Congress** Handover of the WMS flag and close of congress – Auditorium
13:30-14:30	**Lunch and end of congress**

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Neuromuscular Disorders 28 (2018) S76–S76

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Table of location of abstract topics ("The Tomé Table")

https://doi.org/10.1016/j.nmd.2018.07.008
0960-8966

Neuromuscular Disorders 28 (2018) S77–S194

Available online at www.sciencedirect.com

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Neuromuscular Disorders 28 (2018) S77–S194

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Abstracts 2018

NEUROMUSCULAR JUNCTION DEFECTS

I.1

Age-related neuromuscular junction instability: causes and consequences

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A properly functioning neuromuscular junction (NMJ) is essential for locomotion and overall health. The molecular mechanisms of NMJ formation are well established. This process is coordinated by the extracellular matrix molecule agrin, which activates a downstream signaling pathway via the Lrp4-MuSK-Dok7 complex, which in turn triggers the organization of rapsyn-AChR complexes. Highlighting their importance in NMJ maintenance, mutations in genes coding for these molecules cause congenital myasthenic syndrome. Correlative evidence indicates that NMJ structure also deteriorates in sarcopenia, the age-related loss of muscle mass and function. Sarcopenia is the primary cause of frailty and a major contributor to morbidity in the elderly. However, it is unclear whether age-related structural changes to the NMJ reflect changes in NMJ function. Moreover, the molecular mechanisms responsible are yet to be elucidated. We will summarize the current evidence for a functional role of NMJ maintenance in sarcopenia and present data indicating the involvement of the mammalian target of rapamycin (mTOR) pathway. Specifically, we find that sustained activation of mTORC1 de-stabilizes mouse NMJs and impairs neuromuscular transmission. In addition, muscle denervation rapidly precipitates the myopathy in young mice with sustained mTORC1 activation in skeletal muscle. These results suggest that tight control of mTORC1 signaling within myofibers is important for the maintenance of proper NMJ function throughout life.

http://dx.doi.org/10.1016/j.nmd.2018.06.021

I.2

New genes and better treatment for congenital myasthenic syndromes

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The congenital myasthenic syndromes (CMS) are rare inherited disorders of neuromuscular transmission characterised by fatiguable muscle weakness. Their overall prevalence is uncertain but is thought to be in the order of 1 in 100 000 of the population in the UK. They are genetically determined (usually autosomal recessive - so a history of consanguinity is common), non-autoimmune disorders. Remarkable differences in severity occur even within families harboring the same mutation. Although impairment of neuromuscular transmission may often give rise to similar clinical presentation many distinct molecular and cellular mechanisms may be involved. It has become evident over the last ten years that impaired synaptic structure and stability are disease features of equal importance as defects in proteins directly involved in signal transmission. Understanding the molecular mechanisms that underlie impaired synaptic transmission helps guide appropriate and often life-transforming therapy. What has also become evident is that for forms of CMS in which synaptic structure is disrupted, treatment with β2-adrengic receptor agonists is highly effective. Cases where components of the AGRN-LRP4-MUSK-DOK7 AChR clustering pathway are mutated usually respond well to this form of medication. Moreover, in CMS patients and in animal models of CMS long term treatment with pyridostigmine may be detrimental to synaptic structure but can be partially alleviated by treatment with β2-adrengic receptor agonists. The benefit of β2-adrenergic agonists alone or combined with pyridostigmine or 3,4-Diaminopyridine is increasingly becoming an effective part of the repertoire for treating many different subtypes of CMS.

http://dx.doi.org/10.1016/j.nmd.2018.06.022

MYASTHENIA GRAVIS

I.3

From trial-and-error to trials without errors in myasthenia gravis

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Myasthenia gravis (MG) is an acquired autoimmune disorder of the neuromuscular junction, caused by acetylcholine receptor (AChR) antibodies, but also associated with antibodies to MuSK, and in rare cases with antibodies to LRP4, Agrin, or ColQ. In all these disorders the antibodies are thought to be the main culprit that causes the neuromuscular junction dysfunction. The mechanism by which these antibodies affect the function of the neuromuscular junction can vary, and include complement mediated membrane damage, antigenic modulation of surface receptors, direct blocking of ligand binding or the interference with conformational changes. For example, AChR MG is mainly caused by complement activating IgG1 antibodies, while in MuSK MG antibodies are IgG4 and block the MuSK-LRP4 interaction. Aside from a direct effect on the target molecule, also other factors probably determine the severity of the disease and threshold for clinical signs and symptoms in individual patients. One could think of the rate of antibody production, activity of the complement system, differences in regulators of inflammation, or the regenerative capacity of the neuromuscular junction. Most therapies will be directed at one or a few of these factors and therefore often a combination of drugs or interventions are used at different stages of the disease. The most elegant therapy would be to solely correct the production of the pathogenic antibodies, without interference with other immune functions. Most trials, however, have tested agents of which the mode of action is a more general immune suppression, including drugs like ciclosporine, mycophenolate mofetil, or methotrexate. Exacerbation is often treated with plasma exchange, intravenous immunoglobulin or immunoabsorption. A recent trial showed the beneficial effect of thymectomy. More recent trials have focused on specific

interventions directed at components of the immune system, like complement inhibition, blocking of the neonatal Fc receptor, therapies directed at a subset of B cells, or specific surface molecules on lymphocytes. The increasing number of agents and interventions that can be used to treat patients with MG offers hope that we will be able to reach stable remission in a large majority of the patients, using a combination of therapeutic agents depending on the disease activity in the individual patient.

http://dx.doi.org/10.1016/j.nmd.2018.06.023

NEW GENES, FUNCTIONS AND BIOMARKERS

O.1

Recessive mutations in *BET1* and *GOSR2* establish Q-SNARE Golgi-vesicle-transport genes as a cause for congenital muscular dystrophy with epilepsy

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SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complexes are essential for docking and the fusion of vesicle-mediated membrane trafficking. Recessive mutations in Q-SNARE GOSR2 involved in ER to Golgi vesicle transport have been known to cause progressive myoclonus epilepsies and ataxia. Congenital muscular dystrophy (CMD) as a possible manifestation has been reported in a patient with severe *GOSR2* mutations in a WMS poster presentation. We report a 4-year-old male with congenital onset and progressive muscle weakness, feeding difficulties, joint contractures, respiratory insufficiency, ophthalmoparesis, cataracts and seizures. CK levels were elevated (3600-6800 U/L), and brain MRI demonstrated mild white matter abnormalities. WES identified a rare biallelic missense mutation (c.202G>C; p.D68H), predicted to be damaging and to influence splicing, and a truncating mutation (c.134delC; p.A45X) in the GOSR2 interacting ER/Golgi Qc-SNARE vesicle transport gene *BET1*, in which human mutations have not yet been reported. Patient fibroblast western blot revealed a severe reduction of BET1 protein, consistent with reduced BET1 RNA levels seen in muscle RNA sequencing. Immunofluorescent studies in patient fibroblasts showed reduction and failure of BET1 protein to localize to the cis-Golgi. Our data suggest that BET1 and GOSR2 deficiency may lead to impaired Q-SNARE mediated vesicle transport from the ER due to aberrant fusion to the cis-Golgi apparatus, manifesting as CMD with epilepsy. Functional analysis of ER-to-Golgi trafficking in CMD-related GOSR2 and BET1 deficient patient fibroblasts, in addition to yeast studies and in silico modeling of these mutations to analyze SNARE-complex stability and formation, will shed light on this novel CMD disease mechanism. Our data establishes a new CMD/epilepsy gene and confirms that an expanded clinical spectrum of ER/Golgi Q-SNARE gene mutations manifests as CMD with CNS disease including epilepsy.

http://dx.doi.org/10.1016/j.nmd.2018.06.024

O.2

Mutations in fast skeletal troponin C (*TNNC2*) cause contractile dysfunction

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Nemaline myopathy (NEM) is a group of rare muscle diseases caused by mutations in genes encoding proteins associated with the thin filament. However, not all thin filament myopathies manifest with characteristic nemaline rods and the spectrum of clinical manifestations is expanding. Troponin C (TnC) binds to TnT and TnI to form the Tn-complex, which regulates thin filament activation. To date, fast skeletal (fs)TnC has not been implicated in disease. Here, we investigate muscle biopsies of two patients with heterozygous, predicted to be damaging mutations (Patient 1 (P1), 27 yrs: c.100G>T; p.Asp34Tyr & patient 2 (P2), 19 yrs: c.237G>C; p.Met79Ile) in the gene encoding fsTnC (*TNNC2*), manifesting clinically as a unique congenital myopathy. P1 had congenital weakness and vocal cord paralysis requiring tracheostomy, with ptosis, opthalmoplegia, osteopenia and clinical improvement over time. Also, a brother, mother and maternal grandmother, presenting with similar symptoms were found to carry the *TNNC2* mutation. P2 has a milder phenotype, with early respiratory weakness, dysphagia and generalized hypotonia, which improved with age, resulting in normal ambulance with mild proximal weakness at age 19. To investigate the mechanism underlying muscle weakness, we performed contractility measurements on single muscle fibers isolated from patient biopsies. Permeabilized fibers were activated by exogenous calcium. P1 showed atrophied type II and hypertrophied type I fibers (confirmed by histochemical analysis). Absolute and normalized maximal force was decreased in type II and increased in type I fibers. The calcium-sensitivity of force was decreased in type II and increased in type I fibers. P2 showed similar results but less pronounced: a lower decrease in calcium-sensitivity of force in type II fibers, no loss of maximal force and no atrophy in type II fibers. In P1, low angle X-ray diffraction data suggested a compressed thin filament in both fiber types, as suggested by shortening of the actin layer line 6 reflection. X-ray data from P2 showed less pronounced changes. Based on these findings, we propose that the *TNNC2* mutations reduce the calcium sensitivity of force, presumably due to changes in thin filament structure, contributing to muscle weakness in patients. The more severe clinical phenotype of P1 compared to P2 is reflected in the experimental results.

http://dx.doi.org/10.1016/j.nmd.2018.06.025

O.3

A patient-derived iPSC model reveals that genotoxic stresses can be risk factors by increasing the causative DUX4 expression in facio-scapulo-humeral muscular dystrophy

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Facio-scapulo-humeral muscular dystrophy (FSHD) is a genetically inherited disease causing progressive weakness of skeletal muscle with unique clinical features such as asymmetrically affected patterns and large varieties of disease progression. As these aspects cannot be simply explained by the causative mutation, the involvement of environmental factors should be considered. It is known that the genetic backgrounds for both FSHD type 1 (FSHD1) and FSHD type 2 (FSHD2) lead to chromatin relaxation of disease-associated genomic locus, resulting in aberrant gene expression of DUX4, a key factor of FSHD pathogenesis by exerting toxicity against muscle cells. How DUX4 expression is regulated in FSHD remains unclear. Thus, we hypothesized that environmental factors, including oxidative stress, may modulate DUX4 expression. To investigate our hypothesis, firstly we established an FSHD myocyte model by using iPSCs derived from one healthy control, FSHD1 and FSHD2 patients and also generating isogenic control clones from FSHD2 by correcting its causative *SMCHD1* mutation. All those clones efficiently differentiated into myocytes. Importantly, FSHD-derived myocytes, and not healthy nor isogenic control myocytes, showed robust gene expression of DUX4 and its direct downstream targets, confirming that our FSHD model is consistent with previous genetic studies. Then, by using this FSHD myocyte model, we demonstrated that DUX4 expression was increased by oxidative stress, mediated by DNA damage response (DDR), and suppressed by inhibition of ATM, a DDR regulator kinase. We also

found that other types of genotoxic stresses also increased DUX4 expression in FSHD myocytes. In summary, our study provides a new FSHD-iPSC model also applicable to drug discovery, and importantly suggests that oxidative stress and other genotoxic stresses can be risk factors against FSHD patients, which may be partially prevented even by daily behaviors.

http://dx.doi.org/10.1016/j.nmd.2018.06.026

O.4

Single-cell RNA-sequencing in facioscapulohumeral muscular dystrophy disease: etiology and development

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Facioscapulohumeral muscular dystrophy (FSHD) is hallmarked by the sporadic expression of the germline and cleavage-stage transcription factor DUX4 in myonuclei of affected muscle. Despite the sporadic nature of DUX4 expression, its presence in muscle activates a cascade of muscle disrupting events eventually leading to muscle atrophy and apoptosis of affected cells. Yet, with an estimated ratio of 1:100 - 1:1000 nuclei expressing DUX4 in primary myotube cultures, transcriptome analyses have systematically been challenged by the majority of nuclei being negative for DUX4 expression, weakening the DUX4 transcriptome signatures. More elaborate analysis of the FSHD-transcriptome has thus far been facilitated by DUX4-overexpression or DUX4-reporter systems biasing the data towards DUX4-associated pathways and limiting the analysis of non-cell autonomous effects. Identifying the "pure" FSHD transcriptome, i.e. including the study of cell-autonomous and non-cell autonomous DUX4 effects, and unraveling the cascade of events leading to FSHD development, has so far been very difficult. We employed single-cell RNA-sequencing (scRNAseq), combined with pseudotime trajectory modeling, to study FSHD disease etiology and cellular progression in human patient-derived primary myocytes. We identified a small FSHD-specific cell population in all 4 tested FSHD patient-derived primary cultures and detected promising new genes that are likely related to direct and indirect effects of DUX4. Furthermore, capitalizing on the heterogeneity in cellular state in FSHD cell cultures, we employed pseudotime trajectory modeling to generate detailed insights into FSHD etiology and cellular progression. We expect that pseudotime trajectories like our FSHD pseudotime model hold invaluable information not only for studying disease etiology, development and progression, but also for biomarker identification and therapeutic target selection

http://dx.doi.org/10.1016/j.nmd.2018.06.027

O.5

Association of phosphorylated neurofilament heavy chain (pNF-H) with nusinersen treatment of SMA: analyses from the ENDEAR and CHERISH studies

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Neurofilament (NF) isoforms are major structural proteins of the neuronal cytoskeleton and are released into interstitial fluid in significant quantities following axonal damage or neuronal degeneration. These analyses investigated the change in pNF-H levels in participants treated with nusinersen or sham control in the Phase 3, randomized, double-blind, sham-procedure controlled ENDEAR and CHERISH studies. ENDEAR enrolled symptomatic infants aged ≤7 months at screening with infantile-onset SMA; CHERISH enrolled children aged 2–12 years with later-onset SMA. Blood samples were taken pre-dose at key study visits for pharmacokinetic analysis; pNF-H levels were measured in plasma using a pNF-H ELLA assay from ProteinSimple. pNF-H levels declined over time in the nusinersen and sham-control groups. However, decline was continual in the sham-control group vs a greater initial decline with nusinersen treatment followed by stabilization. In ENDEAR, the greatest difference vs the sham-control group was observed at Day 64: percentage change in pNF-H levels was -71.9 (±SE 2.38) for nusinersen vs -16.2 (±8.73) for sham-control. A similar pattern in pNF-H level decline to Day 85 was observed in CHERISH: percentage change was -48.4 (±SE 3.27) vs 6.2 (±6.82) for the nusinersen and sham-control groups, respectively. Correlations between baseline characteristics and pNF-H levels were also assessed. In ENDEAR, baseline log(pNF-H) correlated with baseline CHOP INTEND (r=-0.30; P=0.001), and age of symptom onset (r=-0.20; P=0.034), at SMA diagnosis (r=-0.25; P=0.006), and at first dose (r=-0.24; P=0.011). In CHERISH, baseline pNF-H correlated with baseline weight (r=-0.44) and disease duration (r=-0.64), age at first dose (r=-0.63; all P<0.0001) and baseline upper limb module test score (r=-0.20; P=0.028). These results suggest pNF-H may be associated with SMA disease characteristics at baseline and declines with nusinersen treatment before stabilization. Further validation and additional analyses, including CSF correlations, will contribute to a fuller understanding of the relationship.

http://dx.doi.org/10.1016/j.nmd.2018.06.028

O.6

Free $Mg2^+$ intramuscular concentration determined by combined 31P and 1H NMR spectroscopy as a potential outcome measure in Duchenne muscular dystrophy

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Free intracellular [$Mg2^+$] has been reported to be lower in skeletal muscle of Duchenne muscular dystrophy (DMD) patients. This reduction in [$Mg2^+$] is likely reflecting membrane leakiness and has potentially major consequences due to $Mg2^+$ regulatory role in many cellular processes. Free [$Mg2^+$] determination with 31P NMRS, based on the chemical shift between α- and β-ATP resonances, is highly dependent on a precise knowledge of intracellular pH because of a competition between H^+ and $Mg2^+$ ions for binding with ATP. The pH of DMD patients as determined by the 31P NMRS chemical shift of inorganic phosphate (Pi) is abnormally alkaline, resulting either from compromised dystrophic myocytes or from an expanded interstitial space. In the second scenario, free [$Mg2^+$] might be underestimated. Intracellular pH can be determined using 1H NMRS of carnosine. We took advantage of this 1H NMRS-based intracellular determination to determine whether free intramuscular [$Mg2^+$] is in fact abnormally low in DMD patients. Non-localized 31P NMRS data of 64 DMD (9.9±3.1 yrs) and 67 normal boys (12.7±4.1 yrs) were analyzed from the forearm flexors, the leg extensors or the triceps surae and [$Mg2^+$] and pH were calculated from the αATP-βATP and Pi-PCr chemical shifts, respectively. In a subset of DMD patients and controls, [$Mg2^+$] was also calculated using the pH measured by 1H NMRS. 31P NMRS based pH was significantly increased and free [$Mg2^+$] was significantly lower in all DMD muscles. [$Mg2^+$] was then recalculated with pH values based on 1H NMRS as this gives the real intracellular pH. The 1H NMRS-based pH was normal in a subgroup of DMD patients in contrast to the 31P NMRS-based pH. The corresponding [$Mg2^+$] values were significantly different with the two methods. However, the significant difference in [$Mg2^+$] between DMD patients and controls was preserved even when the intracellular pH was similar in both groups. Low free [$Mg2^+$] was confirmed and a likely consequence of membrane leakiness in DMD patients. This makes [$Mg2^+$] a potential functional biomarker of sarcolemma properties restoration by a therapeutic dystrophin expression.

http://dx.doi.org/10.1016/j.nmd.2018.06.029

LIMB-GIRDLE MUSCULAR DYSTROPHY I

P.1

Limb-girdle muscular dystrophy type 2L: clinical, neurophysiological, and imaging correlation in the first reported Brazilian cases

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The limb-girdle muscular dystrophy type 2L (LGMD2L) is caused by recessive mutations in *ANO5*. The disorder usually involves asymmetrically the scapular muscles, but a distal myopathy is reported too. Other distinctive features are pain following exercises and preferential/more severe male involvement. Despite reports suggesting it as the third most common LGMD in Northern Europe, there is no report of LGMD2L in the Brazillian population. The patients were submitted to neurological evaluation, electroneuromyography (ENMG) and muscle magnetic resonance imaging (MRI). Molecular diagnoses was accomplished through next generation sequencing on DNA samples collected from blood. MRI was performed in Achieva 1.5 T System, Philips Healthcare, The Netherlands, case one: male, 65 years old, born from nonconsanguineous parents, presenting leg pain after exercise and climbing stairs difficulty since 60 years old. NGS showed the *ANO5* variant c.188dup (p.Asn63Lysfs*15) in homozygosity. EMG revealed diffuse myopathy with denervative activity on lower limbs. MRI revealed fatty replacement on posterior leg compartment. Case two: male, 21 years old, born from consanguineous parents, presenting falls since 12 years old. After two years he noted upper limb symptoms. NGS showed the *ANO5* variants c.[259G>A(;)680G>C]; p.[(Val187Ile)(;)(Gly227Ala)]. EMG revealed diffuse myopathy with diffuse denervative activity. MRI revealed common extensor digitorum and soleus fatty replacement. On tight, the posterior compartment was the most affected. Case three: male, 51 years old, born without consanguinity, presenting lower limb weakness since 40 years old. NGS showed the *ANO5* variants c.[188dupA(;)2009A>G];[p.(Asn63Lysfs*15)(;)p.(Tyr670Cys)]. EMG revealed diffuse myopathy with denervative activity on left quadriceps. MRI was not performed, but on physical examination, was evident the calf enlargement. The typical clinical, imaging and EMG findings resulting from *ANO5* gene mutation was found in the reported patients and, despite to be most frequent in Europe, LGMD2L can be found in Brazilian population too.

http://dx.doi.org/10.1016/j.nmd.2018.06.030

P.2

***ANO5* - Three different phenotypes and a new histological pattern**

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Anoctamin 5 (*ANO5*) is a putative intracellular calcium- activated chloride channel. Recessive mutations in *ANO5* cause primary muscle disease, and the clinical spectrum ranges from asymptomatic hyperCKemia and exercise-induced myalgia to proximal and/or distal muscle weakness. The most typical presentation is limb-girdle muscular dystrophy type 2L (LGMD2L). The objective of this work was to describe the clinical, pathological and molecular findings of three unrelated patients with *ANO5* - related muscle dystrophy. To that end, we did a retrospective study, analyzing our database from October 2004 to February 2018 where 1,500 muscle biopsies for diagnostic purposes were performed. Patients were attended by two myology experts, who performed and analyzed muscle biopsies. Muscle biopsies were frozen in cooled isopenthane, cryostat sectioned and stained and reacted routinely (minimum 16 stainings). A custom panel including 115 genes (Nextera Rapid Capture, Illumina) and TruSight One Panel (Clinical Exome, Illumina) was used for NGS sequencing in those cases without a definite pathological diagnosis. All samples were sequenced in a MiSeq (Illumina) platform. As a result, three patients were diagnosed of *ANO5* -related muscle dystrophy, all of them presenting the common exon 5 mutation c.191dup plus a missense mutation in the other allele. They showed three different phenotypes (LGMD2L, distal myopathy and asymptomatic hyperCKemia). Curiously, all three muscle biopsies showed different patterns, but in one of them it was seen numerous ragged-red fibers with little endomysial inflammation and partial invasion cell by T lymphocytes. In conclusion, *ANO5* - related muscle dystrophy is a heterogeneous disease with different clinical phenotypes as we already knew, but also different histological patterns, even mimicking a mitochondrial myopathy. This work widens clinical, histological and anatomo-pathological features related to *ANO5* mutations.

http://dx.doi.org/10.1016/j.nmd.2018.06.031

P.3

Phenotypic spectrum and muscle pathology in a Chinese cohort with *ANO5* recessive mutations

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ANO5 encodes anoctamin-5, an endoplasmic reticulum-associated putative intracellular calcium-activated chloride channel that is highly expressed in skeletal and cardiac muscle and bone. *ANO5* was found to be the causative gene of limb girdle muscular dystrophy type 2L, which was one of the most common forms of muscular dystrophy in Europe. The clinical manifestation ranged from mild symptoms such as asymptomatic hyperCKemia, myalgia, muscle cramps and stiffness, to severe symptoms such as muscle weakness and atrophy, recurrent rhabdomyolysis with the existence of cardiomyopathy. We collect the clinical manifestations, muscle MRI images and muscle pathology in 5 Chinese patients with recessive *ANO5* mutations revealed by targeted next generation sequencing in the past 3 years. The *ANO5* variants (NM_213599) include one reported missense mutation (c.1640G>A p.Arg547Gln) and 5 Novel mutations (c.1103C>T p.Thr368Met, c.1969C>T p.Gln657X, c.2423A>T p.D808V, c.2498T>G p.Met833Arg and c.2596_2597del p.K866fs). The clinical presentations of 5 patients manifested as asymptomatic hyperCkemia, isolated cardiomyopathy and limb-girdle muscle weakness. Muscle MRI revealed selective fatty infiltration in quadriceps femoris, adductor magnus and medial gastrocnemius. Muscle biopsy in three patients showed mild to moderate muscle fiber variation and increased internal nuclei. Subsarcolemmal deposits with PAS positive staining was demonstrated in one old male patient with cardiac involvement. Further western blotting with muscle samples showed mild to moderate reduction of anoctamin-5 protein expression. Taken together, we report a Chinese cohort with recessive *ANO5* mutations, presenting diversified clinical phenotypes affecting the skeletal and cardiac muscles. PAS-positive deposits in skeletal muscles may offer a clue for further investigation on the pathogenesis of anoctamin-5 defect.

http://dx.doi.org/10.1016/j.nmd.2018.06.032

P.4

Axial muscular affection in patients with LGMD2L

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Limb girdle muscular dystrophy, type 2L (LGMD2L) is one of the most common types of the autosomal recessive LGMDs in Europe and characterized by progressive, proximal weakness and atrophy of hip- and shoulder-girdle muscles. Axial muscle affection has not yet been investigated systematically in this patient group. Axial muscles are crucial for the stabilization and mobility of the spine. Involvement of these muscles may influence activities of daily living. To investigate the affection of the paraspinal muscles in LGMD2L-patients, Dixon MRI was performed in patients to quantify the fat fraction of muscle. This study plans to include 15 LGMD-patients. At current stage of the study, the LGMD2L patient group

consisted of five men and three women, aged 44 to 62 years, and twenty-four age-matched controls. All subjects were examined by MRI. Fat fraction was calculated in three positions of paraspinal muscles (erector spinae muscles and multifidus muscle); cervical (C6), thoracal (Th12) and lumbar (L4/L5) and in psoas muscles. To investigate the correlation between affection of paraspinal muscles and lower extremities, the anterior and posterior muscle groups in thigh were examined by Dixon MRI. The preliminary results in this study show that compared to healthy controls, patients with LGMD2L have a significant higher fat fraction in paraspinal muscles at thoracal position ($p = 0.028$):fat fraction was 25.4% in patients vs 18.8% in controls, and lumbar position ($p = 0.0044$):fat fraction was 37.3% in patients vs 26.7% in controls. Furthermore, results indicate no correlation between muscle affection lumbar vs. both anterior and posterior thigh compartments. In conclusion, the study demonstrates that LGMD2L-patients also have axial muscular affection besides the characteristic muscle involvement.

http://dx.doi.org/10.1016/j.nmd.2018.06.033

P.5

Effect of MAPK Inhibition on the differentiation of rhabdomyosarcoma cell line TE671 combined with CRISPR/Cas9 technology: an *in vitro* model for the study of human muscle diseases

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Mouse and rat muscle cell lines can not completely replace research made on human cells. The human rhabdomyosarcoma cell line TE671 has been used extensively to study different aspects of muscle biology. TE671 bears a mutation in the k-RAS gene that produces an increase in Ras activity, a key element in the signal transduction pathway MAPK / ERK. However, the ability of TE671 to differentiate and form myotubes has not been fully explored. In the present study, we examined muscle differentiation when we specifically stopped proliferation of human TE671 (WT-TE671) cells by using 1,4-diamino-2, 3-dicyano-1,4-bis[2-aminophenylthio] butadiene (U0126), a MAP kinase inhibitor. Our data showed that treated cells initiated fusion and myotube formation together with increased expression levels of dysferlin and myogenin. Treatment of WT-TE671 cells with vitamin D3 alone and co-treatment with U0126 and vitamin D3 also promoted dysferlin expression. Vitamin D3 potentiates the expression of dysferlin by: i) non-genomic actions via the MAPK cascade and ii) genomics by binding to the vitamin D receptor located in the promoter of the dysferlin gene. We also knocked out the *DYSF* gene, which is involved in muscle differentiation and its lack in muscle leads to a myopathy, using CRISPR/Cas9 technology in WT-TE671 cells (Dysf-KO TE671). No dysferlin expression was observed before and after U0126 treatment of Dysf-KO TE671. Although myogenin expression was absent in vehicle-treated Dysf-KO TE671 cells, after U0126 treatment, myogenin reached levels similar to WT TE671. This widely available source of human cells appropriately treated with UO126 may represent a useful model to study human muscle differentiation *in vitro*. The design of a new dysferlin-deficient cell line should allow studying pathophysiological pathways involved in dysferlinopathies and constitute a tool for high-throughput screening of compounds for the treatment of these patients and other muscle diseases.

http://dx.doi.org/10.1016/j.nmd.2018.06.034

P.6

Functional recovery by readthrough therapy in a knock-in mouse model with nonsense dysferlin mutation

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Defects in dysferlin gene cause limb-girdle muscular dystrophy 2B or Miyoshi distal myopathy. Nonsense mutations have been reported to be most common among Korean patients with dysferlinopathy. More than half of the patients have at least one nonsense allele in dysferlin. Readthrough by ataluren is a promising strategy to overcome nonsense mutation, in use for the nonsense-mediated Duchenne muscular dystrophy. We generated a knock-in mouse with p.Q832* mutation, most frequently found among our dysferlinopathy cases. Mice with homozygous p.Q832* mutation lost dysferlin expression at sarcolemma. It performed worse on the Rotarod and forelimb grip test than wild type C57BL6 mice and moved less on activity monitoring. On eccentric contraction ex vivo, extensor digitorum longus muscle from these mice tended to break easily. These abnormalities could successfully be alleviated when the mice were orally administered with ataluren in liquid. Furthermore, ataluren decreased the number of damaged muscle, fiber size variation and serum creatine kinase level. This results support that readthrough strategy with ataluren will also be applicable to patients with nonsense dysferlin mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.035

P.7

Proteomic investigation of muscle-derived proteomic biomarkers of dysferlinopathy

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Dysferlinopathy is an autosomal recessive disease caused by a *DYSF* gene mutation and the most common limb-girdle muscular dystrophies in Korea. To objective of the present study is to identify the diagnostic biomarker in dysferlinopathy. We reviewed the medical records of the myopathy database from January 2002 to October 2016. Nine vastus lateralis muscle samples from six patients with dysferlinopathy and three control subjects were enrolled in this study. The six patients with dysferlinopathy were genetically confirmed. We separated proteins/peptides from nine muscle specimens using two-dimensional electrophoresis. For comparison of protein spots, image analysis was carried out in two typical samples which were derived from dysferlinopathy patient and control subject, respectively. Then, we evaluated the expression levels of identified protein spots in six patients and three control subjects. Data acquisition of protein fragmentation pattern was performed by liquid chromatography-mass spectrometry. Finally, we identified 29 differently expressed proteins/peptides. In conclusion, this is the second study showing altered expression of proteins in muscles tissues of patients with dysferlinopathy. Our results provide new insight into the identification of biomarkers of dysferlinopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.036

P.8

Clinical outcome study for dysferlinopathy: three years of natural history data for clinical trial readiness

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The Jain clinical outcome study (COS) is an international study evaluating patients with genetically confirmed dysferlinopathy. 203 patients were re-

cruited across 15 sites and in 8 countries. Dysferlinopathy clinically presents with a spectrum of muscle weakness including both distal and proximal phenotypes which presents significant challenges for developing appropriate clinical trial outcome measures. COS aims to develop understanding of disease progression and identify the most relevant outcome measures for this cohort to facilitate trial readiness in dysferlinopathy. Here we report three years of longitudinal functional data. Patients attended six visits over three years. Physiotherapy medical and MRI assessments were conducted. Physiotherapy assessments included manual muscle testing (MMT) hand held dynamometry (HHD) and functional scales (North Star Assessment for dysferlinopathy and performance of Upper limb), as well as timed tests (rise from floor, 10 metre walk / run, four stair climb and descend; Timed up and go, TUG; Six minute walk distance, 6MWD) and respiratory function testing (forced vital capacity and mouth inspiratory pressure). Functional measures have been evaluated to determine which outcomes are the most sensitive to change in an effort to determine appropriate outcome measures for this heterogeneous population in future clinical trials and permit power calculations to be conducted. The North Star Assessment for dysferlin permitted the stratification of the cohort at baseline and over three years enables the identification of a range of trajectories. Progression in dysferlinopathy can be demonstrated using functional outcomes and dynamometry as measured by physiotherapists over three years. Results support future study design and help power future clinical trials. Further work is required to investigate any modifying factors behind the different trajectories that are apparent.

http://dx.doi.org/10.1016/j.nmd.2018.06.037

P.9

A comparison of the utility between three muscle strength assessment methods in dysferlinopathy

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This study compared results between 3 methods of muscle strength testing used in the jain clinical outcome study (COS) for dysferlinopathy performed at baseline and year 1 visits. The COS is an international natural history study of patients with dysferlinopathy with the intent of improving trial readiness. Dysferlinopathy presents with heterogeneity in muscle weakness, including both distal and proximal phenotypes which poses significant challenges for developing appropriate clinical trial outcome measures. Two hundred and three patients, at 15 sites in 8 countries were evaluated using three methods to measure strength on a variety of upper and lower limb muscle groups. Manual muscle testing (MMT) uses the medical research council scoring system to subjectively grade the amount of resistance the subject can withstand as the evaluator pushes against the extremity. Hand held dynamometry (HHD) uses a force transducer in a small device held against the extremity by the clinical evaluator. Quantitative muscle testing (QMT) uses a force transducer secured to a wall mounted fixed frame. Although MMT is quick, simple and does not require specific equipment, it produces ordinal level data, which can be difficult for statistical analysis. Both HHD and QMT provide objective and quantitative measures of muscle strength but require specific equipment to perform. Cost and the size are significant limitations of QMT. All sites completed MMT and HHD, while only 7 of the 15 sites had the QMT equipment available. Muscle strength changes over 1 year will be presented for each of the three assessment methods. Although HHD, QMT and MMT detected change in many of the same muscles, differences in the responsiveness will be highlighted. Both HHD and QMT options offer linear, objective and quantitative data. HHD is an inexpensive, more accessible and simple option compared to QMT muscle testing. All three methods were able to detect change in this heterogeneous cohort over one year.

http://dx.doi.org/10.1016/j.nmd.2018.06.038

P.10

Imaging phenotype in dysferlinopathy and its relationship with disease duration and disability are unravelled by heatmaps and random forests

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Imaging phenotype of dysferlinopathies has been described, but how muscle imaging pattern changes along the disease evolution and the increasing disability is still to be understood. In a previous report we showed the utility of using MRI to correlate degree and distribution of muscle involvement with functional assessment scores. In this work we analysed the imaging phenotype in dysferlinopathy and its relationship with disease duration and disability, by using heat maps and random forests. Whole-body MRI was performed 33 patients with dysferlinopathy and fibroadipose infiltration of 61 muscles were scored according to Kornblum scale. Scores were represented in a heat map. We trained regressive random forests to predict disease duration, dimension 1 of MFM and modified Rankin scale based on muscle scoring and applied a variable selection algorithm to select the most important muscle scoring for the prediction. Heatmaps helps to delineate a positive and negative fingerprint of dysferlinopathy imaging phenotype. Disease duration is related with fibroadipose infiltration of infraspinatus, teres minor, supraspinatus and flexor digitorum longus. Dimension 1 of MFM increases with higher infiltration of teres minor, triceps, sartorius and adductor magnus and brevis. Modified Rankin scale is related with infiltration of vastus medialis, gracilis, infraspinatus and sartorius. Our work demonstrates the positive and negative fingerprints in dysferlinopathy. Thigh muscle and specially, upper limb muscle infiltration may be important markers of disease progression in dysferlinopathy and should be considered in planning future studies with quantitative MRI in the affected patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.039

P.11

Clinical outcome study in dysferlinopathy: random forest approach to assess the relationship between baseline muscle MRI and longitudinal functional outcome measures

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The Jain clinical outcome study (COS) is an international study of 203 adults with dysferlinopathy in 8 countries. Patients undergo six visits over three years, during which physiotherapy and medical assessments as well as muscle MRI were performed. Our aim is to analyse baseline muscle pathology by MRI in a large cohort of dysferlinopathy patients and to examine the relationship between baseline muscle MRI findings and the results of longitudinal functional outcome measures over one year. We aim to identify which muscles may predict a rapid decline over one year. Lower limb muscle MRI has been performed in 182 patients with a confirmed diagnosis of dysferlinopathy in 14 different centres, using 1.5T or 3T scanners from different manufacturers (Philips, General Electrics, Siemens). 74 patients also underwent upper limb muscle MRI at baseline. Muscles were scored on axial T1-weighted sequences with the semi quantitative Mercuri visual scale modified by fisher. Physiotherapy assessments included muscle strength (manual muscle testing; hand held dynamometry) and functional ability evaluations (adapted north star, brooke test, timed tests) and patient reported outcome measure (ACTIVLIM). We will present the outcome of the analysis between semi-quantitative MRI at baseline and disease progression over one year as measured by the north star assessment for dysferlinopathy, the 10 metre walk and the ACTIVLIM using the Random Forest approach (package "random forest SRC" in R). Random-forest studies will be used to identify whether combinations of muscle involvement at baseline can predict a change of more than 10% in muscle function tests at a one year visit. Muscle MRI is useful for the diagnosis of patients with muscle disorders, but also to identify patients at risk of having a quick progression of their symptoms.

http://dx.doi.org/10.1016/j.nmd.2018.06.040

P.12

Clinical outcome study in dysferlinopathy: medical comorbidities and polytherapy in a large population of dysferlinopathy patients

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The Jain clinical outcome study (COS) is the largest international natural history study in patients with genetically confirmed dysferlinopathy. We describe the comorbidities in a large cohort of COS patients and also analyse the drugs and supplements taken during this natural history study. 203 patients (aged 12-88) have been recruited across 15 sites in 8 countries. All patients were molecularly diagnosed and followed over 3 years. Medical history and comorbidities were collected by specific questionnaires administered by trained nurses or medical doctors. Medication used were categorised using the British National Formulary. The most common comorbidities at baseline were: cardiovascular (33 patients-16%-; 27 of which are hypertension), endocrine (21 patients-10%-; 10 of which are hypothyroidism) and respiratory (16 patients-7%-; 15 if which are asthma). 5 patients were diagnosed from autoimmune diseases. During follow-up, hypertension was diagnosed in 6 patients. 141 patients (69%) were taking drugs or supplements at the beginning of COS (range: 0-10 medications). 65 patients (32%) were on daily vitamins or nutritional supplements, 27 (13%) on anti-hypertensive, 25 on NSAIDs (12%), 16 (8%) on opioids and 16 (8%) on antidepressants. During follow-up, anti-hypertensive, antidepressants, opioids and anti-epileptic prescribed more commonly than other medications. Of note, before participation in COS and due to misdiagnosis with inflammatory myopathies, 56 patients (28%) had previously been treated with steroids, 16 (8%) with ivIg and 12 (6%) with immune suppressants. Hypertension, asthma and hypothyroidism are the most common comorbidities in COS. Besides vitamins and supplements, anti-hypertensive, NSAIDs, opioids and antidepressants are the most prescribed drugs. 28% of the patients had previously taken steroids due to misdiagnosis. We believe this information should be taken into account when designing interventional clinical trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.041

P.13

Rasch analysis of the individualised neuromuscular Quality of Life Questionnaire administered to patients with dysferlinopathy

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Our objective was to assess the psychometric properties of the Individualized Neuromuscular Quality of Life Questionnaire administered to adults with dysferlinopathy. 203 patients with dysferlinopathy were recruited to participate in the Jain Foundation's International Clinical Outcomes Study for dysferlinopathy. Quality of Life Questionnaires conducted at baseline, year 1,2,3 and 4 were included. The psychometric properties of the instrument were examined using Rasch analysis. A total of 660 questionnaires were completed. 24 of 39 items displayed disordered thresholds and model misfit was identified in 19 of 39 questions (mean item fit residual 0.649, SD: 3.039). Item dependency was high (Shown in 33 pairs of items) and the mean person fit residual was estimated at -0.094 (SD: 1.703). The Person Separation Index were estimated at 0.954 and 0.915. Unidimensionality was not acceptable. The INQoL questionnaire does not appear to be a suitable measure of health-related Quality of Life in adults with dysferlinopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.042

DUCHENNE MUSCULAR DYSTROPHY – CLINICAL

P.14

The profile of Duchenne muscular dystrophy patients younger than 10 years old from KUKAS registry, Turkey

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This study was performed to update the informative data and identify the general profiles of Duchenne muscular dystrophy (DMD) patients under 10 years in National Registry of Neuromuscular Diseases (KUKAS) located at Hacettepe University. The informative data of the patients were obtained by questionnaire method. The questionnaire consists of two parts. The first part consisted of questions about mutations, height, weights, length percentiles according to age, the age to start walking, functional levels, mental status, steroid use, and cardiomyopathy. The second part included the social facilities of the family and children. The families answered the questions by telephone

interview. Of the 1,100 DMD patients enrolled in the KUKAS system, 434 were under 10 years of age. Three hundred fifty one of these patients were reached. The mean age of the patients was 88 ± 31 months. Body weight and mean height were 25 ± 9 kg, 117 ± 18 cm, respectively. While 90 children were under the 3rd centile, 57 were over the 97th centile. The genetic information of the patients were as follows; 44 patients (12%) have a deletion in exon 51, 30 (8%) in exon 53, 17 (4%) in exon 45, and 23 (6%) patients have a nonsense mutation. Two-hundred and four patients (58%) have been on steroids and 17 (5%) of the total patients have been diagnosed with a type of cardiac disease. The intellectual disability was found in 54 of 351 patients (16%). Ten percent of the patients were using wheelchair. When the socio-economic and educational status of the families were considered, the monthly income of the families was found to be 2.716±2.387 Turkish liras. The square meters where they live in were mean 122±33 meters. Primary school was the graduation degree of 167 mothers (50%) and 123 fathers (37%). One hundred sixtyeight children (50%) with DMD declared that they had not a private room in their homes and 251 of children (76%) were complained about the stairs of the building they live. The number of household members were 4 of 156 (46%). One-hundred and sixty patients (47%) have one sibling while 10 (3%) have more than 4 siblings. While the medical conditions of the patients showed parallelism to the natural history of the disease, they were not advantageous in terms of physical and social conditions.

http://dx.doi.org/10.1016/j.nmd.2018.06.043

P.15

First report of natural history and survival in patients with Duchenne muscular dystrophy in Zimbabwe: a retrospective cohort study

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Recent advancement in treatment of Duchenne muscular dystrophy (DMD) has achieved outstanding results with significant improvement in survival and ambulation in developed countries. Recently, males affected with DMD were identified in Zimbabwe through efforts of missionary team. We aimed to describe the status of diagnosis, natural history and challenges in management of these boys with DMD through the collaborative effort of humanitarian organizations, Muscular dystrophy center of Zimbabwe and Muscular dystrophy center at the University of Minnesota. We retrospectively reviewed and curated data from a cohort of 24 affected males with DMD ranging from 8 to 20 years of age over a period of 3 years. We report natural history and management of these patients. There is a marked delay in recognition of first symptoms and diagnosis in majority of patients. In this cohort, 75% of the affected males had family history of an at least one affected male, representing 14 families. We identified genetic variants in some affected males. The mean age of loss of ambulation was 10.3+/-1.5 years and the mean age at death was 17.8+/-2.4 years. All affected males were steroid naïve. Medical and humanitarian efforts included placing boys in the group home, training local care givers, providing wheelchairs and orthotics. The medical team started 5 patients on prednisone and 6 non-ambulatory patients on BiPAPs. Our report brings awareness of current state of health in males with DMD in Zimbabwe. Healthcare disparity due to poverty, political instability and lack of appropriate medical care results in inadequate treatment of males affected with DMD. The life span of the affected males is shorter than in the same patient population in developed countries. Humanitarian support and training of local care givers with improved access to medical care according to the published care standards may improve general health, quality of life and extend the life span of affected males.

http://dx.doi.org/10.1016/j.nmd.2018.06.044

P.16

Epidemiology, clinical and genetic features of Duchenne disease in Portugal: A multicentre retrospective study

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Duchenne muscular dystrophy (DMD) is the most common form of inherited muscle disease in childhood, with an estimated incidence of 1 in 3500 boys. In Portugal, there is no actual epidemiological data regarding the incidence and natural story of patients with DMD. Although steroids probably modify the natural history of DMD by improving strength, time of autonomous deambulation, pulmonary and cardiac function, there is still a paucity of high-quality data on their long-term efficacy. Other controversies about age of beginning, duration and dosing of steroids are still under discussion. Identify patients with Duchenne disease in Portugal, collecting diagnostic age, onset and steroid scheme age, loss of deambulation, ventilatory support and cardiac involvement. We collected data from patients observed in Portuguese tertiary hospitals from january 2015 to december 2016. We identified 142 cases, 104 in pediatric age and 38 adults. The mean age in 2016 was 13,4y (3-40, median 14). Global mean age at diagnosis was 4,7y (4m-12y, median 5y); in group of patients older than 18 years was 5, 9y (1-12y, median 6y); in group under 10 was 2,86y(4m-7y, median 2y). The actual mean time of follow up was 10,7y. Genetic study was available in 129 patients and we found 74 deletions (57%), 19 (15%) duplications and 36 mutations (28%). The vast majority of patients was on steroids (99 out 133) in several different schemes. The mean start age was 5,9y (2-12; median 6). In this group, time of deambulation loose was 10,63y (7-18; median 10), and mean age of ventilatory support was 14,5y (9-24, median 14). Within the group of patients not treated with steroids mean age of loss of deambulation was 9,72 years (7-14; median 10) and mean age of ventilatory support was 18,4 years (11-31; median 18). Mean age in two groups differ considerably (treated 13,4y; not treated 21,9y). In our study, age of diagnosis decreased, especially in last decade which is similar to other referral centers. About 28% of patients have mutations emphasizing the need for proceeding genetic testing when MLPA is negative. Steroid treatment seems to increase ambulatory age nearly one year. Nevertheless, the two groups arenǵ comparable because no treated group are older and probably select for the least severe forms of disease (that survive around years independently of treatment).

http://dx.doi.org/10.1016/j.nmd.2018.06.045

P.17

Reasons for first visit to neurologists in Chinese patients with dystrophinopathy: a survey study

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The genetic screening for dystrophinopathy is controversial, but early diagnosis is important for patients to receive appropriate treatment without delay. Some cost-effective methods are necessary to achieve this goal. We designed this study to investigate the reasons for first visit to neurologists in Chinese patients with dystrophinopathy and provide some valuable information about screening. 224 patients with dystrophinopathy were given questionnaire surveys which consisted of basic information and reasons for visiting neurologists initially. The results indicated that accidental finding of elevated levels of serum aminotransferases or creatine kinase (CK) accounted for 54.46% of reasons for first visit (25.89% for abnormal aminotransferases; 27.68% for abnormal CK; 0.89% for both abnormal indexes) and the complaint of motor dysfunction for rest of the participants. Furthermore, the ages of first visit between patients with different reasons were significantly different [3.61 (2.23 - 4.74) in patients complaining about elevated levels of

serum enzymes versus 7.50 (6.15 - 9.84) in patients complaining about motor dysfunction, $p < 0.001$]. As to the reasons for obtaining the detections of serum enzymes, 53.66% of them got the abnormal results during the entrance medical examination of kindergarten and 42.28% of them obtained the examinations because of other diseases, and the rest of them (4.07%) forgot the detailed reasons. Among the 52 patients obtained the detections of serum enzymes due to other diseases, respiratory tract infection (38.46%) and hand-foot-mouth disease (17.31%) were common reasons for the detections. Elevated levels of CK and aminotransferases were the main reason for first visit. Before obvious motor dysfunction occurs, the serum enzyme test is helpful to indicate the disease. Furthermore, more than half of patients obtained the test during the entrance medical examination of kindergarten, which is useful but not early enough for dystrophinopathy. Thus, the policy of earlier screening for dystrophinopathy needs to be discussed further. In conclusion, aminotransferase and CK offer great capacities to screen dystrophinopathy in China, which is useful for early diagnosis.

http://dx.doi.org/10.1016/j.nmd.2018.06.046

P.18

The importance of nutrition in Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a severe progressive muscular dystrophy caused by mutations in the DMD gene, leading to the absence of a functional dystrophin protein. Besides muscle problems, metabolic, gastrointestinal (GI), and resulting nutritional issues contribute to the pathology. This aspect of the disease is often neglected. Assessment by a dietician should be part of routine check-ups. In early stages, overweight, caused in part by corticosteroid use, is common and, together with the primary deficit in dystrophin, affects muscle and whole body metabolism. In later stages patients are at risk of undernutrition, e.g. due to problems with swallowing and chewing. When the disease progresses, GI issues, including constipation, metabolic acidosis, gastroparesis, and reflux, are often seen. The precise role of nutrition and metabolic problems has not been well-studied. There is a need for natural history data, including dietary data, and good outcome measures regarding body composition, tailored to DMD patients. Furthermore, few well-designed studies, both preclinical and clinical, into the use of dietary supplements and on nutrient requirements have been performed. Good guidelines for maintaining a healthy weight and nutritional intake are currently lacking. Additionally, the risk/benefit ratio of high doses of over-the-counter supplements, their effect on different muscle types and potential interactions with other medicines require more detailed investigation. Families should be encouraged to speak with the clinical team and the pharmacist. The importance of fluid intake and dental hygiene should be stressed as well. Guidelines for diet and supplements need to take into account the stage of the disease and background culture, and be readily accessible in understandable formats, such as short videos and one-page explanations. It may also be helpful to provide examples of recipes and alternatives to make implementation of dietary change in daily life easier.

http://dx.doi.org/10.1016/j.nmd.2018.06.047

P.19

Prevalence of metabolic disorders in patients with Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a severe muscular disease inherited in a recessive X-linked pattern and characterized by progressive loss of functional muscle mass followed by changes in body composition. Finding diagnostic markers and determining adequate nutritional support remain a challenge. To describe metabolic disorders in DMD patients followed-up at a tertiary care center A prospective, observational, cross-sectional study was conducted. Anthropometric measurements were taken evaluating body composition (bioelectrical impedance analysis), and biochemical parameters in all DMD patients seen between June 2013 and April2014 who agreed to participate in the study. 63 boys between 5.4 and 18.7 years of age were evaluated. Diagnosis of obesity ranged from 28% measuring body mass indexZ-score (BMI Z-score) to 70% using percentage of fat-free mass (%FFM). Of all patients, 29% presented with insulin resistance (IR) associated with BMI Z-score and waist circumference. Of these patients, 77% were obese according to the BMI Z-score and 83% were on steroid treatment. Acanthosis was found to be associated with IR (p 0.04). None of the patients had impaired fasting glucose nor diabetes. Dyslipidemia was found in 40% of the DMD patients, due to hypertriglyceridemia in 90%. A high prevalence of obesity was observed. BMI Z-score underestimates the diagnosis of obesity. No correlation was found between steroid type and body composition or metabolic disorders.

http://dx.doi.org/10.1016/j.nmd.2018.06.048

P.20

Cognitive performance in Duchenne muscular dystrophy

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Duchenne muscular dystrophy causes motor function impairment, due to symmetrical progressive muscle weakness. However, cognition may also be affected in about one-third of boys with Duchenne muscular dystrophy. The intelligence quotient is the gold-standard measure of cognition, but other tests can be used to evaluate and describe the cognitive performance. This study aimed to describe the cognitive performance of children and adolescents with Duchenne muscular dystrophy and to investigate possible relationships between cognitive and motor outcomes. In addition, the present study proposes the use of relatively simple screening tests, which can be applied by a wide range of health professionals. Ninety-nine people with Duchenne muscular dystrophy and fifty age-matched healthy controls participated. All participants were 6-17 years old and regularly attended schools. They were evaluated with the Wechsler intelligence scale for children, the verbal fluency test (saying animals´names in one minute), the digits test (repeating digits in direct and reverse orders) and the Motor Function Measure. The Duchenne muscular dystrophy group showed heterogeneous cognitive and motor performance. There were significant differences between the groups in the Wechsler intelligence scale for children, the verbal fluency test and in the direct order of the digits test ($p<0.050$ in all comparisons). There was no significant difference in the reverse order of the digits test ($p=0.434$). There was no correlation between motor and cognitive performance. The cognitive performance of people with Duchenne muscular dystrophy was poorer than the performance of the control group. There was no difference in the reverse order digits test, which can be explained by the high difficulty showed by both groups. The evaluation protocol was feasible to evaluate boys with Duchenne muscular dystrophy. The verbal fluency test and the direct order of the digits test detected differences between boys with Duchenne muscular dystrophy and controls and can be useful screening tests in clinical practice.

http://dx.doi.org/10.1016/j.nmd.2018.06.049

P.21

Changes over years in the verbal IQ of patients with Duchenne muscular dystrophy

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Previous studies have shown that the average IQ of patients with Duchenne muscular dystrophy (DMD) was 70-80 and that 30% had an intellectual disability; nevertheless, most published studies are cross-sectional. In the present study, we investigated changes over years in the intelligence of patients with DMD using a cross-sectional study with an aim of examining future needs for support. The subjects were 25 patients with DMD (14 admitted, 11 at home) who underwent multiple Wechsler Intelligence Scale (WAIS-R or WAIS-III and WISC-III) tests between January 1st 2002 and December 31st 2017 while they were long-term residents of our facility or followed up at our facility. Progress was examined using the verbal IQ (VIQ) results of the Wechsler Intelligence Scale. The average VIQ in the multiple tests of 25 study participants was 77.3 (±4.2).Of these, 36% had a VIQ of ≤69. The average VIQ during initial testing was 75.7 (±4.2), and the average VIQ during final testing was 79.7 (±4.3), making +4.0 the mean difference. When observed over time, the VIQ of many patients did not decline. The average age during the initial exam was 14.9 years (range, 6.9–31.0 years), and the average age during the final exam was 21.9 years (range, 9.5–37.3 years). The average examination interval was 6.9 years (range,1.5-14.2 years). When the results were examined comparing at-home patients and inpatients, the average VIQ for inpatients was 67.8 (±5.0), whereas for at-home patients it was 89.3 (±5.2). The average VIQ was 67 (±5.2) during initial examination of inpatients, and the average VIQ was 70 (±5) during final examination; the mean change value was + 3.0. The average VIQ was 86.7 (±5.7) during initial examination of at-home patients, and the average VIQ was 92.0 (±5.9) during final examination; the mean change value was +5.3.In patients with DMD, physical and cardiac functions decline over years, but intelligence is indicated to be maintained . In recent years, the average lifespan of patients with DMD has lengthened, and with active support for schooling and employment, they may be able to live lives suited to their individual abilities. The deteriorating physical functions are thought to be augmented by the use of welfare devices and self-help tools as well as by caregivers carefully considering teaching materials and instructional methods.

http://dx.doi.org/10.1016/j.nmd.2018.06.050

P.22

Evaluation of methylphenidate in males with Duchenne muscular dystrophy and a comorbid attention deficit hyperactivity disorder: a preliminary study

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Attention deficit-hyperactivity disorder (ADHD) is a common comorbidity of Duchenne muscular dystrophy (DMD). Until now, treatment with methylphenidate (MPH) has never been described before in patients with DMD and ADHD. Our aim was to evaluate the effectiveness and safety of MPH in males with DMD and a comorbid ADHD. Neuropsychological (cognition and behavior) and medical (cardiac follow-up, medication interactions and side-effects) data of a clinical sample of ten males (mean age = 8.1 years, range 6.3- 9.8) with DMD and a comorbid ADHD diagnosis was retrospectively analyzed at baseline (T0; without MPH), short-term follow-up (T1; with MPH; mean interval T0-T1 = 8.3 months, range 4.3-15.6), and long-term follow-up (T2; mean interval T1-T2 = 23.1 months, range 2.6 – 77.7). An initial MPH dose of 5mg/day was given, with an increase of 2,5-5 mg/week depending on individual tolerance, and treatment response, until a sufficiently effective dose was reached (up to 0,2 – 0,6 mg/kg/day). At T1, results demonstrated an improvement in attention (i.e. concentration, impulsivity, and distractibility) in four patients. Suboptimal effects were reported in four patients, and no effects in two patients. At T2, 70% of the patients considerably improved in attention with MPH treatment. No major (cardiac) side effects were reported. One patient discontinued treatment due to mood problems. Overall, our data show that MPH treatment can be clinically effective and safe in males with DMD and a comorbid ADHD diagnosis, with close regular monitoring of medical and neuropsychological effects. However, the development and use of DMD specific cognitive and behavioral measurements with adequate sensitivity to objectively evaluate the effect of MPH is of crucial value.

http://dx.doi.org/10.1016/j.nmd.2018.06.051

P.23

Longitudinal follow-up of verbal working memory and processing speed in males with Duchenne muscular dystrophy

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Neurocognitive deficits are frequently described in Duchenne muscular dystrophy (DMD), but little is known on whether it improves or worsens over time within individuals. The aims were to (1) longitudinally assess verbal working memory and information processing speed, and (2) investigate a genotype-phenotype relationship. Thirty-three (3.7 to 17.3 years old) males with DMD completed a verbal working memory and non-motor speed of information processing test twice, with a mean interval of 30.4 months (range 7.3 – 59.3). Participants were divided in three subgroups based on presence of dystrophin isoform Dp140 (a) Dp140-; n=15, (b) Dp140+; n=11, or (c) undeterminable n=7. In comparison to normative data, the DMD group scored low on verbal working memory, but not on processing speed. Raw scores of both tests increased over time, while (normative) scaled scores remained the same indicating a normal growth curve, although functioning is below the general population mean for working memory specifically. The Dp140+ group scored higher on both tests at T0 compared to the Dp140- group, however this was not the case at T1. It is concluded that males with DMD lag behind in verbal working memory, but not in processing speed. This delay is consistent, with some improvement on T1 relative to T0 as appropriate for increasing age. Additionally, a difference in developmental curve is suggested for the Dp140+ group compared to the Dp140- group, which may support a genotype-phenotype relation in DMD cognitive performance.

http://dx.doi.org/10.1016/j.nmd.2018.06.052

P.24

Cognition and cerebral structural abnormalities in dystrophinopathies

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Cognitive and behavioural abnormalities are a hallmark of dystrophinopathies (DMD/BMD), but little is known about the possible neuroanatomical substrates. To determine the frequency and pattern of intellectual abilities in patients with BMD/DMD, as well as to investigate potential anatomical substrate of these manifestations. 20 patients with DMD/BMD were submitted to the WISC-IV scale. For each subject, volumetric T1 cerebral sequences were obtained in a 3T MRI scanner. A control group of 11 age-matched healthy boys was used for comparison. We computed cortical thickness measurements using the Free Surfer software. Between-group comparisons were performed with generalized linear model taking total intracranial volumes as covariate. Uncorrected p values <0.05 were considered significant. Results: There were 17 DMD and 3 BMD patients. Mean age and disease duration were 10.7±2.2 and 6.4±2.5 years, respectively. Six patients were wheelchair-bound at the time of evaluation. Genetic profile encompassed large deletions/duplications and nonsense mutations. WISC-IV revealed 9 patients (45%) with intellectual coefficient (IQ) below 70, hence

categorized as intellectually impaired. Among them, 2 DMD boys had IQ between 35-45 and 7 had IQ>45. IQ mean values for the remaining patients was 88. Working memory (89%) and perceptual organization (56%) were the domains more frequently impaired. We found cortical thinning at the left superior parietal and right frontomarginal gyri (p=0.005 and 0.006, respectively). We identified a higher frequency of intellectual deficits in our patients with DMD/BMD than generally reported in the literature. Frontal and parietal atrophy were found, which may underlie the cognitive abnormalities found. Larger cohorts are needed to validate these findings.

http://dx.doi.org/10.1016/j.nmd.2018.06.053

P.25

Circadian rhythms in young boys with Duchenne muscular dystrophy

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Research has determined that the circadian timing system exerts temporal control over physiology, and its alteration has been associated with several systemic symptoms, including fatigue, appetite loss and poor sleep. However, the clinical impact of circadian disruption in young boys with DMD has not been empirically studied. In fact, there is little to no clinical data on sleep disturbances in very young boys with DMD, although such disturbances have been observed in typically developing children and older boys with DMD. Moreover, current research suggests children with hereditary disorders are rarely evaluated for sleep quality, hence rarely provided with sleep interventions or strategies. We have enrolled 35 boys with DMD and their caregivers throughout the U.S. to explore sleep and daily activity over a 30-day period. We have observed low levels of sleep efficiency, high levels of sleep fragmentation, and erratic behavior in the young boys' circadian rest-activity rhythms. Circadian rhythm disturbances may represent a potential vulnerability marker for emergence of numerous bio-behavioral problems, and thus, rest/activity rhythm stabilization has promise to inform early-identification and prevention/ intervention strategies for young boys with DMD. Through longitudinally and objectively measuring and monitoring daytime activity and nighttime sleep patterns in young boys with DMD, we have determined the need to explore family-based interventions tailored for children to achieve optimum sleep. We are also studying known relationships between cognition, physical function, and other bio-behavioral outcomes in our young boys with DMD. It is highly likely that results from this study will inform sleep interventions in other young populations with disability.

http://dx.doi.org/10.1016/j.nmd.2018.06.054

P.27

Descriptive characteristics of males with Duchenne muscular dystrophy using insurance claims data

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Patients with DMD typically use steroids, as well as support devices such as wheelchairs, ventilators and airway clearance devices. In the U.S., real-world healthcare utilization and costs for DMD are not well known. A retrospective study of healthcare claims for male patients (6 to 25 years old) presumed to have DMD (between 2001 and 2014) was performed using Truven Health Analytics MarketScan® Commercial (non-government insurance claims, approximately 30 million U.S. patients) and Medicaid (government insurance claims, approximately 8 million U.S. patients) databases. Patients with ≥2 medical claims and diagnosis for hereditary progressive muscular dystrophy (HPMD-ICD-9-CM: 359.1) were included (no specific ICD-9 code for DMD), with date of first diagnosis being the index date. Patients were stratified by age (6-10, 11-14, 15-18 and 19-25 years). Clinical characteristics, treatment patterns, and healthcare utilization were assessed in the 12 months following index date, compared to a non-DMD, age-matched cohort. A total of 2285 patients were presumed to have DMD (1137 = commercial; 1148 = Medicaid). Fractures were present in all DMD age groups (highest in 15-18 age group: 15.2%). Sleep issues were also common in all cohorts and increased with age (10.3% in the 6-10 year and 20.6% in the 19-25 year commercial group). Steroid use was just over 43% in the 6-10 age commercial group (excludes deflazacort, since it was not FDA approved during the evaluation period), but fell to 12.3% in the 15-18 years age group. Anti-infective drug use was common among all DMD age cohorts and increased across age groups. Average annual cost of all healthcare services increased with age; the highest costs were seen in the 11-14 year commercial cohort ($33,344 (SD = $81,070) and in the 15-18 year Medicaid cohort ($58,411 (SD= $293,493)). In this retrospective study, DMD patients had higher disease burden and annual HCRU costs when compared to non-DMD, age-matched cohorts.

http://dx.doi.org/10.1016/j.nmd.2018.06.055

P.28

The adult DMD patient: new challenges for an emerging phenotype

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The introduction of steroid treatment and non-invasive ventilation (NIV) in Duchenne muscular dystrophy (DMD) has resulted in increased life expectancy. DMD is no longer a pediatric disease. Patients are now transitioning to adult life. In this context new clinical problems are being recognized, some of them extremely serious and potentially fatal. Understanding this new emerging phenotype is key to anticipating problems and further optimizing patient care. We reviewed medical records of DMD patients 25 years and older from our database. Clinical characteristics and the development of complications were analyzed. The cohort was divided into living (LP) and deceased patients (DP). For statistical analysis we used t-test. 46 patients. 34 (LP) (29,9±3,17 years); 12 (DP) (29,16±3,85 years) (p=0,5). Age at onset of steroids was 9,5±3,95 (LP) and 14±6,89 (DP) (p=0,01). Age at loss of ambulation was 15,51±4,07 (LP) and 12,41±4,56 (DP) (p=0,03). Age at onset of NIV was 26,29±4,08 (AP) and 21,28±4,15 (DP) (p=0,018). Swallowing difficulties were present in 38% of all patients. 3 patients developed severe intestinal obstruction (fecaloma) requiring hospitalization, 1 died due to intestinal perforation. 2 patients developed sudden decompensation due to minor trauma, requiring inotropic and ventilatory support. 56% of patients were depressed. In this cohort, adults with DMD, earlier onset of steroid treatment was associated with later loss of ambulation and NIV requirement. New disease manifestations, not observed in pediatric populations, broaden phenotypic expressions. Minor clinical situations can lead to serious, even fatal complications. Chronic constipation and fecaloma formations are potentially fatal. Sudden, severe decompensation may occur in patients with no history of significant heart or respiratory failure. Swallowing disorders start appearing. Depression is highly prevalent among adults with DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.056

P.29

Analysis of respiratory function of Duchenne muscular dystrophy with Chilaiditi syndrome

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Chilaiditi syndrome (CS) may cause respiratory symptoms that are worsened in a seated position. Constipation is one of the exacerbation factors in CS and laxatives is effective when CS causes the respiratory symptoms. We have reported a case of CS in a patient with Duchenne muscular dystrophy (DMD), complicated with constipation, the incidence and effects of CS on respiratory function in such patients remain unknown. We investigated the

prevalence of CS and occurrence of constipation requiring treatment among patients with DMD, as well as the effect of posture on respiratory function. Methods/Patients: We retrospectively reviewed medical records, chest X-ray, and respiratory function data obtained between 2007 and 2018 for patients with DMD aged over 15 years. Patients who had vital capacity (VC) data in both supine and seated positions were included. Patients in whom the colon was shown to be interposed between the diaphragm and liver on chest X-ray were assigned to the CS group, and the remainder to the non-CS group. Ninety seven cases were enrolled in this study. Six cases (6.2%) were diagnosed with CS. Four cases (66.7%) with CS and 14 cases (15.4%) without CS were treated for constipation using laxatives. In all CS cases, seated VC was on average 14% lower than supine VC. The case with the lowest VC showed dyspnea only while seated. Among the 91 cases (93.8%) without CS, seated VC was higher than supine VC in 55 cases (60.4%). In the non-CS group, seated VC was on average 3.2% higher than supine VC. Although previous studies have shown that seated VC is higher than supine VC in DMD, patients with CS tended to have lower VC while seated than while supine. The complication of constipation was more common among DMD patients with CS than those without CS. The clinicians should monitor respiratory function when CS is identified. If the patients with CS show dyspnea while seated, CS may need to be treated with laxatives.

http://dx.doi.org/10.1016/j.nmd.2018.06.057

P.30

Guidance regarding use of implantable cardioverter-defibrillators in Duchenne and Becker muscular dystrophy

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With increases in survival by addressing pulmonary complications, cardiomyopathy is a leading cause of mortality in Becker/Duchenne muscular dystrophy (DMD). Current adult implantable cardioverter-defibrillator (ICD) guidelines list as a class I indication that ICD implant is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35% and who are in NYHA functional Class II or III. There are no guidelines for ICD therapy for nonischemic cardiomyopathy in adolescents with DMD. The purpose of this study was to determine the incidence of arrhythmias and sudden cardiac death in the DMD/BMD population to guide ICD indications. This international study (8 centers) identified subjects with DMD and an EF < 55% and/or ICD. Data obtained included: demographics, clinical arrhythmias, medications, echocardiograms, and interrogations from implanted devices. We identified 124 pts with an average age of 21 (range 10 -51) years and a mean EF of 37% (range 6-55). Forty nine patients had an EF < 35%. 17 patients had arrhythmias: Non-sustained VT (12), Atrial tachycardia (2), Atrial Flutter (3), SVT (2). Nine pts had ICDs implanted, 7 of whom had an EF < 35%, none of which fired for ventricular arrhythmias. Twelve patients died, three of whom had ICDs. One patient with an ICD died suddenly and interrogation demonstrated no tachyarrhythmia. Despite 49 % of patients having a low EF, clinical arrhythmia in DMD is unusual. Non-sustained VT was found in 10% (35% of patients with EF< 35). None of our patients died from sudden cardiac arrest. None of the patients with ICDs had an appropriate ICD discharge. This data suggests that adult ICD guidelines of ICD for EF <35% should be used cautiously and in conjunction with the fact that sudden arrhythmic cardiac death is unlikely in this inherited cardiomyopathy cohort of pediatric and young adult patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.058

DUCHENNE MUSCULAR DYSTROPHY – IMAGING AND BIOMARKERS

P.31

Serum creatinine: a promising biomarker for distinguishing Duchenne muscular dystrophy from Becker muscular dystrophy in patients aged ≤ 3 Years

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Dystrophinopathy is a common muscular dystrophy, consisting of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD). The prognosis and treatment strategy between DMD and BMD are totally different. This study was designed to investigate correlations between the level of serum creatinine and clinical phenotypes of dystrophinopathy in young patients. We enrolled sixty-eight patients with dystrophinopathy, whose diagnosis were based on clinical manifestation, biochemical changes, and molecular analysis. The levels of serum creatinine were determined when patients were ≤ 3 years old. Each patient was followed up, and motor function and clinical phenotype were assessed when the same patients were ≥ 4 years old. The results indicated that in young patients, lower serum creatinine levels were associated with increased disease severity ($p < 0.01$), and that serum creatinine levels were the highest in patients exhibiting mild BMD ($p < 0.001$) and the lowest in patients with DMD ($p < 0.01$), and were significantly higher in patients carrying in-frame mutations than in patients carrying out-of-frame mutations ($p < 0.001$). Serum creatinine level cut-off values for identifying mild BMD [18 μmol/L; area under the curve (AUC): 0.947; $p < 0.001$] and DMD (17 μmol/L; AUC: 0.837; $p < 0.001$) were established. These results suggest that serum creatinine might be a promising biomarker for distinguishing DMD from BMD in patients aged ≤ 3 years and could assist in the selection of appropriate treatment strategies.

http://dx.doi.org/10.1016/j.nmd.2018.06.059

P.32

Chemokine CXCL12 and osteopontin are highly expressed in Duchenne muscular dystrophy patients

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Muscle satellite cell is muscle progenitor cell, which generates myoblast to repair wounded skeletal myofiber. Regeneration occurs efficiently with help of muscle-resident mesenchymal progenitor cells. In last-this meeting, we showed transplantation of bone marrow-derived mesenchymal stromal cells (Bm-MSCs) also facilitated muscle regeneration in Duchenne muscular dystrophy (DMD) model mice, which lead to drastic efficacy against death-related symptoms. Moreover, we showed the efficacy was attributed to chemokine CXCL12 and osteopontin (OPN) secreted from Bm-MSCs, which affected on self-renew of muscle satellite cell and myoblast fusion in muscle regeneration, respectively. We showed the importance of CXCL12 and OPN in skeletal muscle regeneration in mouse model; however, the relevance of these factors to human skeletal muscle diseases remains unclear. Plasma concentration of CXCL12 and OPN were measured by human CXCL12/SDF-1 alpha Quantikine ELISA kit and human osteopontin Quantikine ELISA kit (R & D systems). The blood test was carried out for 20 DMD patients and 10 healthy volunteers. All analyses were approved by institutional review board. We determined statistical differences by means of Student's t test. Descriptive statistical analyses were performed with SPSS software. CXCL12-plasma concentration in healthy subjects and DMD patients were (mean [±SD]) 2040 ± 440 pg/mL vs. 2430 ± 370 pg/mL; $p = 0.016$. OPN concentration in healthy subjects and DMD patients were 15.0 ± 5.0 ng/mL vs. 19.4 ± 3.0 ng/mL; $p = 0.026$. On the other hand, we could find no correlation of each

factor concentration with creatine kinase value among DMD patients. Compared with healthy subjects, both CXCL12 and OPN, which are well-known tissue-remodeling factor, are highly expressed in DMD patients. CXCL12 and OPN seem relevant to human skeletal muscle diseases. As biological factors commonly play a role in diverse cellular functions, in order to elucidate the roles of CXCL12 and OPN in muscle, we should know their states in various myopathies and aged muscles.

http://dx.doi.org/10.1016/j.nmd.2018.06.060

P.33

Skeletal muscle T1 mapping correlates with MFM scores in dystrophinopathies

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Dystrophinopathies are a group of degenerative and progressive genetic diseases, which compromise the skeletal and cardiac striated muscles and still have no cure, leading to death. With advances in the management of the disease, it's necessary to have objective parameters in monitoring its progression and therapeutic effectiveness. To determine T1 signal intensity in muscle magnetic resonance imaging (mMRI) in patients with Duchenne and Becker muscular dystrophy (DMD/BMD), correlating with clinical data and time of disease. To define which muscles are most affected. Twenty-one patients were clinically evaluated through the Motor Function Measure (MFM). The mMRI images were obtained in the muscles: biceps, triceps, quadriceps, gastrocnemius and soleus, bilaterally. The T1 intensity was measured with Horos software. A strong correlation was observed between T1 hypersignal and total MFM (MFM-T) in the muscles: gastrocnemius, soleus, triceps and biceps ($r > 0.5$). Among these, the biceps, triceps and soleus are more related to the changes in MFM-D2, while the gastrocnemius are more associated with changes in MFM-D1 and MFM-D2. The quadriceps did not show correlation with MFM-T or its domains. No correlation was found between T1 hypersignal and time of disease (p value> 0.05). Quadriceps was the most affected muscle on both sides. Patients with DMD and DMB have an increased T1 intensity, the greater the liposubstitution. The T1 hypersignal is a simple, fast, reproducible and non-invasive quantitative technique that does not require sophisticated software to be calculated. Nowadays, with new therapeutics and others still in progress, this data could be useful in patients selection and follow-up in clinical trials. It also could be used outpatient, due to its strong correlation with MFM in most of the muscles evaluated.

http://dx.doi.org/10.1016/j.nmd.2018.06.061

P.34

MR biomarkers in imaging DMD clinical trial network

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MR biomarkers have shown considerable promise as outcome measures in clinical trials for Duchenne muscular dystrophy (DMD). Imaging DMD has developed an extensive clinical trial network with an infrastructure that enables high quality MR data collection across centers. The infrastructure incorporates standardized acquisition procedures, efficient data management, automated processing of images and spectra as a pipeline, phantoms, and quality assurance procedures. MR procedures have been successfully implemented for measuring fat fraction (FF) by both magnetic resonance spectroscopy (1H-MRS) and Dixon imaging, as well as the MRI transverse relaxation time constant (T2), enabling cross validation among measures. In addition, we measure 1H2O T2 using single voxel 1H-MRS as a marker of membrane stability and inflammation. In this study, we describe the infrastructure and MR methods used in these studies, and compare the sensitivity of these measurements to disease progression in a range of lower extremity muscles and ages using data acquired at three centers using 3T MR systems in 138 individuals with DMD (8.8 ± 3.3 years) and 51 unaffected controls (8.8 ± 2.4 years). Our results show a range of involvement and disease progression among muscles, with each MR measure able to robustly discriminate unaffected controls and DMD ($p < 0.05$). Furthermore, the MR measures of muscle FF and MRI T2 were all able to detect longitudinal changes within one year ($p < 0.05$) in the soleus and vastus lateralis. Overall, the Imaging DMD Clinical Trial Network has successfully implemented standardized MR procedures over multiple sites, and presently includes 21 certified MR sites across North America and Europe.

http://dx.doi.org/10.1016/j.nmd.2018.06.062

P.35

Higher MRI muscle fat fraction at similar age is associated with earlier loss of ambulation in Duchenne muscular dystrophy

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Full market-approved drugs are lacking in Duchenne muscular dystrophy (DMD). MRI muscle fat fraction (FF) is a potential surrogate endpoint in clinical trials but is acceptable to regulators only if related to clinically meaningful milestones. Any biological parameter that consistently changes with age will inherently correlate with functional parameters in a progressive disease. It is thus imperative for such a parameter to have additional predictive value to age in order to function as biomarker. We aimed to assess the additive predictive value of vastus lateralis (VL) FF to age on loss of ambulation (LoA). 3-point Dixon images of the right thigh of DMD patients were acquired at CCHMC at 0, 6, 12 and 18 months and at LUMC at 0, 12, 24 and 30 months, between 2013 and 2016. Regions of interest were drawn by two independent observers on multiple slices covering 70 mm around the VL center, defined as the most proximal slice where the biceps femoris short head was visible. Mean weighted VL FF's were fitted to a logistic growth-model to predict FF from 0-20 years of age, with only the slopes of the FF curves differing per patient. Month and year of LoA for non-ambulant, and last follow-up for ambulant patients, were determined by taking a thorough history between July 2017 and March 2018. Baseline FF's from the observers were compared using an intraclass correlation coefficient (ICC) with a two-way random model and Bland-Altman analysis. A Cox model was fitted for the time to LoA with predicted VL FF as the only (time-varying) covariate. At least one datapoint was available for 34 DMD patients (mean baseline age 10.3 years, range 5.5-16.1). 7 patients were non-ambulant at baseline and 31 used corticosteroids. Between first MRI and March 2018, LoA occurred in 10 DMD patients. Baseline ICC of the observers was 1.00 with a bias of 0.03% (limits of agreement -1.23 to 1.29). The hazard ratio of a percent increase in VL FF for the time to LoA was estimated at 1.10 (95% confidence interval 1.05-1.14) which was highly significant (Wald test, $p < 0.001$). Vastus lateralis fat fraction has a significant additive predictive value to age on the date of loss of ambulation. This supports quantitative MRI as an alternative endpoint for clinical trials in DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.063

P.36

Early impact on disease identified for Ezutromid using magnetic resonance spectroscopy (MRS) in Duchenne muscular dystrophy

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Clinical trials in DMD require prolonged treatment durations to demonstrate slowing of the disease trajectory through functional tests. Quantitative MRS is a disease biomarker technology that may be an earlier predictor of drug effect; recent publications demonstrate its correlation to function. PhaseOut DMD is a Phase 2 open-label study evaluating ezutromid, a potential first-in-class utrophin modulator, administered to 40 ambulatory DMD patients who were all on stable corticosteroids. Primary endpoints (48 week) are MRS assessments. Two MRS endpoints were considered – water relaxation time (T2) and fat fraction (FF), for which drug effects have been reported at 3 and 12 months, respectively. Results of 24-week interim analysis have been reported. At baseline, mean (SD) T2 in the soleus muscle was 31.9 (1.9) ms (n=40); correlation coefficients (CC) with functional endpoints were all <0.3. Mean (SD) FF in the vastus lateralis (VL) muscle was 15.0% (13.38) (n=39). Baseline CC with functional endpoints (NSAA, 6MWD, 10 m walk/run and time to stand) ranged from -0.192 to 0.642. By week 12, a mean decrease from baseline in MRS-T2 in the soleus muscle was observed (-0.66 msec); by week 24, the decrease was statistically significant: average reduction was -0.86 ms (95% CI-1.44, -0.28; n=38). In untreated boys with DMD, MRS T2 does not change significantly over 1 year. An overall small increase in VL FF (+3.8%, n=37) was observed at 24 weeks; increases in FF are expected over time with annual average of +5 to +10%. The baseline data support the reported natural history regarding correlation of MRS FF to function. Interim data, after 24 weeks of ezutromid, indicate the potential for early identification of drug effects on disease progression. Results from the 48 week read-out will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.064

P.37

Upper extremity quantitative muscle ultrasound is related to disease severity in boys with Duchenne muscular dystrophy

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With an increasing amount of non-ambulant boys with Duchenne muscular dystrophy (DMD), objective and child-friendly outcome measures are necessary to evaluate upper limb function in boys with DMD. The primary aim of this study was to assess the relation between upper extremity quantitative muscle ultrasound (QMUS) and disease severity in boys with DMD. Additionally, reference values of QMUS were collected in healthy boys and the effect of age on QMUS was compared between healthy boys and boys with DMD. Finally, reliability was assessed in a subgroup of both groups (12 healthy boys and 10 boys with DMD). Echo intensity (EI) and muscle thickness (MT) of the upper limb measured by QMUS were determined in 71 healthy boys and 43 boys with DMD (mean age 12.45 and 12.41 years). Clinical assessments (upper extremity muscle strength (MS), Brooke scale, Performance of upper limb (PUL) and Motor Function Measure Dimension 3 (MFM-D3)) were performed in boys with DMD only. The effect of age on QMUS was assessed using linear regression analysis. The relation between QMUS and clinical assessments was assessed using correlation coefficients. ICC's were constructed to determine inter-rater and test-retest reliability. EI was higher and increased with age in boys with DMD whereas in healthy boys EI was independent of age. MT increased with age in healthy boys whereas age did not influence MT in boys with DMD. A higher EI was related to decreased performance on Brooke scale, PUL and MS of shoulder abductors. A lower MT was related to decreased performance on Brooke scale and MS of shoulder abductors. This study found excellent inter-rater reliability of EI in healthy boys, which is in accordance with previous literature. Poor test-retest reliability of EI was found in both healthy boys and boys with DMD. QMUS of the upper extremity is related to disease severity in boys with DMD. Therefore, this study establishes QMUS of the upper extremity as an objective, relevant outcome measure in DMD which is not influenced by fatigue, verbal understanding or patient cooperation.

http://dx.doi.org/10.1016/j.nmd.2018.06.065

P.38

Description of Becker muscular dystrophy cardiomyopathy natural history by cardiac magnetic resonance imaging from the first to third decades provides insight for cardiac surveillance

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Cardiomyopathy is the leading cause of mortality for Becker muscular dystrophy (BMD) patients and is characterized by fibrosis accumulation leading to left ventricular ejection fraction (LVEF) decline. Risk stratification is challenging due to the wide variation of cardiomyopathy onset, progression and severity. Additionally, cardiomyopathy may be the first disease manifestation without evident skeletal myopathy. Current guidelines recommend "complete cardiac evaluation" at ten years of age, but do not dictate the imaging modality. Little advanced imaging data for young BMD patients is available to guide cardiac surveillance. We thus sought to describe the early natural history of BMD cardiomyopathy. We retrospectively reviewed cardiac MRI (CMR) data from 39 patients, aged 7 to 25 years, who had a combined 84 complete studies including late gadolinium enhancement (LGE). At our center, all BMD patients undergo CMR when sedation is no longer necessary. Of 13 patients under 15 years of age, undergoing a total 25 CMR studies, no patient had evidence of LGE or an abnormal LVEF (<55%). 26 patients, aged 15-25 years,underwent a total of 59 CMR studies. We reviewed the first study obtained for cross-sectional analysis. No patients in the <15 year old group overlapped with this group. The mean age of initial study was 18.3 years (+/- 3.0). 12/26 (46%) first time studies were LGE positive and 6/26 (23%) had an abnormal LVEF. All patients with abnormal LVEF were LGE+, significant by chi-square analysis. In a sub-analysis of mutations involving the amino-terminal dystrophin gene exons, 3/5 (60%) of 15-25 year old first time scans demonstrated +LGE. These 3/5 studies had a median age of 17.8 years (range 15.7-22.0) and median LVEF of 48 (range 47-54). This data set adds to the early natural history of BMD Cardiomyopathy, potentially guiding decision making regarding when to obtain a first-time cardiac MRI in young patients with BMD. No currently actionable cardiomyopathy was identified under 15 years of age. These observations should be interpreted with caution given the low prevalence of this disease process and sample size studied. Notably, significant cardiomyopathy was already evident by CMR in many 15-25 year old young men with BMD. Further studies should clarify the role of fibrosis and other risk factors in predicting LVEF and clinical outcome measures.

http://dx.doi.org/10.1016/j.nmd.2018.06.066

CONGENITAL MYOPATHIES: GENERAL AND RYR1

P.39

Congenital cytoplasmic body myopathy – a nosological clarification

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Cytoplasmic bodies (CB), thought to be derivatives of Z-discs, are frequent, but most often non-specific findings in biopsied human muscle. They occur frequently in Hereditary Myopathy with Early Respiratory Failure (HMERF) due to mutations in the titin gene (*TTN*). When numerously encountered in muscle fibers they have, in the past, been given rise to descriptions as "myopathy with cytoplasmic bodies" or "cytoplasmic body myopathy". Only very recently CB have been associated in a clinically severe myopathy with a heterozygous mutation in the *ACTA1* gene, but without any nemaline bodies suggesting that an entity "congenital cytoplasmic body Myopathy" indeed exists. In this presentation we corroborate this suggestion by reporting a now 54-year-old female patient whose clinical and myopathological findings had been reported 37 years ago, and who has now been found to have a novel heterozygous *ACTA1* mutation. This patient had experienced developmental delay, muscle hypotonia, generalized muscle weakness and slender build, numerous cytoplasmic bodies in her biopsied muscle fibers and near-total type 1 fiber predominance, but no rods at the age of

15 years. By adding this nosography to "congenital cytoplasmic body myopathy", we also expand the clinical and genetic spectrum of this congenital myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.067

P.40

The distinct clinical phenotype of *PIEZO2* loss of function

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PIEZO2 is a widely expressed stretch-gated ion channel recently shown to mediate human mechanosensation. We recently recognized a unique and consistent clinical phenotype with selective sensory deficits as well as systemic manifestations in two individuals with loss of function mutations in the *PIEZO2* gene. We gathered detailed phenotypic information on six unrelated patients aged 10 to 19 years with genetically confirmed biallelic inactivating mutations in *PIEZO2*. Detailed sensory assessment, electrophysiological testing, musculoskeletal, respiratory, gastrointestinal and urological evaluations were conducted. All six patients presented with neonatal hypotonia, hip dislocation, joint hypermobility and contractures. There was transient respiratory distress in the newborn period and feeding difficulties as well as evidence of impaired gastrointestinal transit and bladder function. Motor milestones were delayed with acquisition of independent ambulation in late childhood, as late as seventeen years of age in one patient in the absence of muscle weakness, while there was progressive scoliosis in all. All patients had a striking absence of joint proprioception, of vibration and glabrous skin touch discrimination, while other sensory modalities were largely preserved. All patients displayed slow improvement in motor coordination, suggestive of a maturational process that recruits and relies on mostly visual compensatory sensory input. The PIEZO2-loss of function phenotype is highly specific and clinically recognizable. While advancing our understanding of human mechanosensation its diagnosis also allows for the development and implementation of rehabilitative measures aimed at recruiting intact sensory modalities in order to compensate for specific deficits and optimize function.

http://dx.doi.org/10.1016/j.nmd.2018.06.068

P.41

Dominant *TNNC2* mutations cause a distinct congenital myopathy with vocal cord paralysis, ophthalmoplegia and clinical improvement over time

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Mutations in genes that impair sarcomeric force generation and affect muscle contraction cause myopathies of variable severity. *TNNC2* encodes fast skeletal troponin C, an important component of the troponin complex, for which human disease mutations have not yet been reported. Here we report two families with a distinct, dominantly-inherited congenital myopathy with rare, heterozygous, predicted-to-be-damaging mutations in *TNNC2*. Patient 1 (P1) of Family 1 (F1) is a 26-year-old male who presented with maternal polyhydramnios treated with serial amniocenteses, significant congenital onset weakness, vocal cord paralysis and respiratory insufficiency requiring tracheostomy until 4 years, severe gastroesophageal reflux, requiring G-tube feeding until 16 years, ptosis, and ophthalmoplegia. At 26 years, proximal strength was 4-/5 (MRC grade), and pulmonary function tests revealed a forced vital capacity (FVC) of 54% predicted. Muscle biopsy showed mild type 2 fiber atrophy, mild variation in fiber size and occasional atrophic fibers. P1′s family history is significant for a brother, mother and maternal grandmother sharing a consistent clinical phenotype. P2 is a 19-year-old female who also presented with maternal polyhydramnios treated with serial amniocenteses, congenital onset weakness, hypotonia and swallowing difficulties requiring G-tube feeding. At 19 years, proximal strength was 4/5, and FVC was 76% predicted. Muscle biopsy showed type 1 fiber predominance and type 2 fiber atrophy. WES was performed in both families and identified a c.100G>T; p.Asp34Tyr mutation in *TNNC2*, segregating with all affected relatives of F1, and a *de novo* c.237G>C; p.Met79Ile mutation in *TNNC2* in P2. Thus, the clinical phenotype of troponin C-related congenital myopathy is notable for polyhydramnios during gestational development, congenital weakness and severe respiratory involvement with significant clinical improvement over time, suggestive of a critical developmental role for *TNNC2*.

http://dx.doi.org/10.1016/j.nmd.2018.06.069

P.42

Congenital hyporegenerative microcytic anemia of unknown origin with XMEA-like muscle pathology

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We received the thigh muscle biopsy of a 55 month old boy diagnosed with congenital hyporegenerative microcytic anemia of unknown origin to investigate for a possible mitochondrial cytopathy. He is the second child from a non-consanguineous couple born in the 32+2 week of pregnancy via cesarean section due to pathological CTG after receiving 7 erythrocyte transfusions in utero. His brother is healthy as are his parents. Hypertelorism, low-set ears and cryptorchidism were described at birth as were muscular hypotonia, truncal ataxia and global developmental delay in the following months. His height, weight and head circumference dropped below the 3rd percentile in the first year of life. Imaging studies found delayed brain myelination, likely haemangioma and iron overload of the liver as well as splenomegaly. Episodes of foul smelling but otherwise normal-appearing urine were reported, but extensive laboratory work-up as well as two bone marrow samples, chromosomal analysis and whole exome sequencing excluded known inherited erythrocyte disorders such as thalassaemia and failed to clarify the underlying condition. His CK was elevated minimally once but normal on all other measurements. ECG, TTE and cardiac MRI were normal. Muscle histology revealed selective atrophy of type I and hypertrophy of type II fibres with vacuolar changes and basophilic spots in particular in the atrophic fibres. In acid phosphatase, alizarin red and unspecific esterase stains as well as in immunohistochemistry with antibodies against membrane attack complex (C5b9), lysosome-associated membrane protein 2 and (sub)sarcolemmal structural proteins, these showed the appearance of autophagic vacuoles with sarcolemmal features (AVSF). Reanalysing exome data with respect to *VMA21*, *LAMP2*, *GAA* and *HNRNPDL* failed to detect abnormalities, as did the biochemical analysis of respiratory chain complexes I and IV as well as the search for deletions of mitochondrial DNA. We seek further cases with this unusual combination of signs.

http://dx.doi.org/10.1016/j.nmd.2018.06.070

P.43

Prevalence of cytoplasmic bodies in a large series of diagnostic paediatric muscle biopsies

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Cytoplasmic bodies (CB) in skeletal muscle biopsies typically appear as discrete, small sarcoplasmic inclusions that are eosinophilic and stain red with Gomori Trichrome (GT). The first description of CB as structural Z-disc anomalies was in 1969, and their association with desmin-related neuromuscular diseases (NMD) was recognised in the 1980s. Since then CB have been reported in association with a range of unrelated neuromuscular disorders, many of these in the pre-molecular era. The aim of our study was to look at the prevalence of CB in paediatric-onset NMD (0-16 years) and any particular genotypic correlation. A natural language search on the pathology database revealed documentation of CB in 41/1000 biopsies (0.04%) referred to our centre (2008-2017). Based on the tinctorial stains (Haematoxylin and Eosin (HE)/GT), frequency of CB was graded semiquantitatively (0, sparse: 1+, <5 fibres: 2+, >5 fibres: 3+, >10 fibres: 4+). The 41 cases with CB featured a variety of pathological diagnoses: centronuclear myopathy with/without cores (4/41), myofibrillar/protein aggregation myopathy (6/41), muscular dystrophy (5/41), nemaline myopathy (8/41), type II atrophy (2/41), neurogenic or mixed neurogenic-myopathic (2/41), mitochondrial myopathy (1/41), non-specific myopathy (12/41) and minimal change (1/41). CB were confirmed ultrastructurally in 5/21 cases, with similar light microscopic morphology of CB in cases with and without ultrastructural confirmation. CB were more frequent (3+) in the centronuclear myopathy group and a proportion of nemaline (3/8) and myofibrillar/protein aggregation (4/6) myopathies. 18/41 cases had a genetic diagnosis (*BAG3, FHL1, CFL2, KHL40, LMOD3, NEB, MYH2, MYH7, RYR1, TTN, STAC3, RAPSYN, DMD, LMNA*, and in one case translocation t(9;11)). In conclusion, CB are a rare finding in paediatric muscle biopsies. They do not provide specific clues for an underlying gene defect and are probably non-specific indicators of myofibrillar modification.

http://dx.doi.org/10.1016/j.nmd.2018.06.071

P.44

Mutations in the myomaker gene causes Carey-Fineman-Ziter syndrome with muscle fiber hypertrophy

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Carey-Fineman-Ziter syndrome (CFZS) is an autosomal recessive inherited disorder presenting as a congenital myopathy with marked facial weakness and variable other features such as facial dysmorphism, hand and foot deformities, joint contractures and growth delay. The causative gene defect was recently identified as variants in *MYMK*, which encodes the myomaker protein that is essential for myoblast fusion during the early development of skeletal muscle. We describe three siblings with CFZS who are compound heterozygous for a recurrent variant in *MYMK*, p.(Pro91Thr) and a novel variant p.(Trp79Arg). All siblings had a marked and characteristic facial weakness and variable dysmorphic features affecting the face, hands, and feet, and short stature. They had experienced muscle hypotonia and generalised mild muscle weakness since early childhood. Repeat muscle biopsies in two of the siblings at ages ranging from 11 months to 18 years of age disclosed, as the only major abnormality at all ages, a marked hypertrophy of both type-1 and type-2 fibers with more than twice the diameter of that in age-matched controls. Our study expands the genetic and clinical spectrum of *MYMK* mutations and CFZS. The marked muscle fiber hypertrophy identified from early childhood in spite of apparently normal muscle bulk, indicates that defective fusion of myoblast during embryonic muscle development results in reduced number of muscle fibers with compensatory hypertrophy and muscle weakness.

http://dx.doi.org/10.1016/j.nmd.2018.06.072

P.45

A new congenital myopathy with multiple structured cores

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Congenital myopathies are a heterogeneous group of inherited muscle disorders characterised by the presence of distinctive morphological features on skeletal muscle biopsy. Cores myopathies show the presence of cores, corresponding to well-delimited rounded areas devoid of oxidative staining. AD *RYR1* and *MYH7* gene mutations have been found in central core and eccentric cores disease patients. Nevertheless, several cores myopathy patients remain genetically unsolved. Our patient was the third child born to healthy non-consanguineous parents. He had mild hypotonia and sucking difficulties at birth. At two months, he developed progressive cardiac failure spontaneously resolved at 6 month. Successive cardiac follow-up was normal. The patient developed progressive diffuse weakness and scoliosis with normal cognitive skills. He underwent Achilles tendons tenotomy at 14 years and arthrodesis at 16 years, followed by gait loss. He showed progressive respiratory involvement and he underwent tracheostomy at 35 years. Last clinical examination at 46 years revealed profound amyotrophy, bilateral ptosis, mild facial weakness, nasal speech and high-arched palate. There was a profound proximal and distal muscle weakness (2 to 3 MRC), and axial weakness of neck flexor and extensor (2 MRC). Whole body MRI demonstrated diffuse and severe muscle atrophy and fat replacement. The respected muscles where masseter, pterigoidian, shoulder rotators, right biceps and triceps, pelvic girdle and bilateral hamstring muscles. Muscle biopsy of the left deltoid at 9 years demonstrated the presence of multiple and well defined round areas devoid of oxidative staining in every muscle fibers, and type 1 fibers uniformity. Muscle biopsy of left radialis muscle at 46 years revealed great fiber size variability with the presence of numerous small fibers. Oxidative staining disclosed the presence multiple core areas often clustered at the periphery of muscle fibers. Electron microscopy studies of both muscle biopsies showed multiple and large areas composed by 'out or register' sarcomeres with jagged Z-lines, corresponding to structured core lesions. Exome sequencing failed to reveal pathogenic mutations in the known myopathies genes. In conclusion we described a congenital myopathy with atypical multiple structured cores not linked to *RYR1* and *MYH7* genes.

http://dx.doi.org/10.1016/j.nmd.2018.06.073

P.46

Novel *ASCC1* mutations causing prenatal-onset muscle weakness with arthrogryposis and congenital bone fractures

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Congenital myopathies affect children and adults in all populations. They are genetically and clinically heterogeneous with a marked variability in severity and disease progression, and patients can manifest additional non-muscle features affecting different tissues. We established a clinically homogeneous cohort of patients with a severe condition characterized by fetal hypokinesia, neonatal hypotonia, respiratory distress, arthrogryposis, and congenital bone fractures, and all deceased shortly after birth. The biopsies of the patients displayed common histological features as fiber size variability and intense oxidative rings beneath the sarcolemma, and electron microscopy revealed disorganized myofibrils with scattered remnants of sarcomeres and enlarged Z-bands. Through exome sequencing, we identified novel recessive *ASCC1* nonsense and frameshift mutations in three families with a total of six affected infants, and segregation of the mutations with the disease was confirmed in all available family members. *ASCC1* codes for a protein of the tetrameric ASC-1 cointegrator complex, composed of ASCC1, ASCC2, ASCC3, and TRIP4. Transcriptional cointegrators act as coactivators or corepressors through the integration of transcription factors in multi-protein complexes, and can thereby modulate gene expression in a tissue-specific way. A single homozygous mutation in *ASCC1* has recently been reported in two

families with a severe and muscle and bone disorder, allowing only a narrow view on the clinical and genetic spectrum of the disorder. Our work expands the *ASCC1* mutation spectrum, and identifies subsarcolemmal oxidative rings and enlarged Z-bands as potential histopathological hallmarks of the disorder. Our findings also emphasize the physiological importance of the ASC-1 complex in fetal muscle and bone development, and pave the way for the molecular diagnosis of further *ASCC1* cases.

http://dx.doi.org/10.1016/j.nmd.2018.06.074

P.47

ASC1-related myopathy is associated with defects in myoblast proliferation and muscle growth: defining the phenotypic spectrum and understanding the pathogenesis of an emerging congenital myopathy

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We recently reported that mutations leading to absence of the poorly characterized transcriptional coactivator ASC-1 (Activating Signal Cointegrator–1), never previously associated with muscle function, cause a novel form of autosomal recessive congenital muscle disease. In 4 patients from a consanguineous family, we identified a homozygous nonsense mutation of the *TRIP4* gene, encoding the ubiquitous ASC-1 protein. Patients presented with congenital muscle weakness predominantly involving axial muscles, lethal respiratory failure, skin abnormalities and joint hyperlaxity without contractures. The mutation resulted in TRIP4 mRNA decay to around 10% of control levels and absence of detectable protein in patient cells. Depletion of ASC-1 in cultured muscle cells from a patient and in Trip4 knocked-down C2C12 led to a significant reduction in myotube diameter ex vivo and *in vitro*, without changes in fusion index or markers of initial myogenic differentiation. To delineate the phenotypic spectrum of this novel myopathy, we report here the clinical and histological findings in 3 additional families with different *TRIP4* mutations. Also, we reveal a previously unsuspected role of ASC-1 in regulating cell cycle progression, as well as myoblast proliferation and size, via modulation of the expression of cell cycle regulatory proteins. ASC-1 absence is associated with shortening of the G0/G1 phase of the cell cycle, leading to accelerated cell cycle progression and altered proliferative capacity of myogenic cells, which can contribute to explain the antenatal phenotype in patients. These results expand the spectrum of ASC1-related myopathy and improve our understanding of its pathophysiology, revealing ASC-1 role in two stages of the myogenic process, myoblast proliferation and myotube growth. Thus, they underline and expand the interest of ASC-1 as a novel and critical regulator of muscle mass and function, and as a potential target to increase or restore muscle growth.

http://dx.doi.org/10.1016/j.nmd.2018.06.075

P.48

Hypercontractile congenital muscle stiffness

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Tropomyosin 3 encoded by the *TPM3* gene is a member of the acting binding tropomyosin family, a component of the sarcomeric thin filaments troponin/ tropomyosin complex that is essential in muscle contraction by regulating the calcium dependent binding of the myosin head to the actin filament. Mutations in *TPM3* cause a clinical and histopathological heterogeneous group of neuromuscular disorders characterized by congenital hypotonia and weakness that includes cap myopathy, congenital fiber type disproportion and nemaline myopathy. Recently, a new phenotype characterized by hypercontractile stats and stiffness was described, most probably due to mutations that increase calcium sensitivity of the troponin-tropomyosin complex, resulting in excessively sensitized excitation-contraction coupling of the contractile apparatus. This study presents the case of a one-year-old female, daughter of non-consanguineous parents, of an uneventful gestation, was born full term with Apgar 3/8 and presented generalized hypertonia and hip dysplasia from the first month of life. She had no cephalic support and was not able to sit without support because of the stiffness. Apparently, she has normal cognition. She has a short neck, hypertrophy of the cervical, paravertebral and proximal muscles of the upper limbs and a bell-shaped chest. During the neurological exam, she was able to move against gravity with all four limbs, but the strength scale evaluation was impaired due to by the stiffness. Deeper tendon reflexes, sensation and cranial nerves were normal. The first diagnosis was Schwartz Jampel syndrome; however, myotonic discharges were not detected in the electromyography exam. Computed tomography of the brain, pelvic girdle radiography, serum CK level, and mucopolysaccharidosis screen were normal. Echocardiogram showed patent foramen oval with left-right flow. Ultrasound of the hip joint showed dysplasia on the left side. Clinical, phenotypic and pathophysiological spectrum of TPM3 mutations are broader than once thought, and now joins congenital hypercontractile and stiffness phenotype.

http://dx.doi.org/10.1016/j.nmd.2018.06.076

P.49

Redefining the morphological spectrum of *RYR1* recessive myopathies

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The *RYR1* gene encodes the ryanodine receptor1, a Ca2+ channel expressed on sarcoplasmic reticulum membranes at the triad junction of skeletal muscle fibres. Dominant mutations lead to CCD and MHS phenotypes whereas recessives manifest with a wide range of clinical and morphological presentation. We present a monocentric revision of muscle biopsies from more than 50 genetically confirmed *RYR1* recessive patients. We performed histological, immunohistochemical and ultrastructural analysis of 58 muscle biopsies from 53 patients. Moreover, levels of RYR1 expression in muscle biopsies have been assessed by Western Blot (WB) and its pertinence with genetics background, clinical severity and morphological findings has been investigated. By optic microscopy, 10 muscle biopsies showed typical cores (single or multiple, central or eccentric) and 6 core and rods association in the same biopsy. Five biopsies showed isolated type1 uniformity/predominance with or without mild myofibrillar disorganization. Most of muscle biopsies presented a unique histological feature characterized by association of irregular myofibrillar disorganization, granular cytoplasmic material deposition, type1 fiber predominance and nuclear internalization and centralization. In rare cases these findings were observed just in few muscle fibers. One third of these cases the myofibrillar pathway presented a targetoid appearance by oxidative stains in variable number of fibers. In one case both the latter histological presentation and cores were simultaneously present. By electron microscopy, typical cores, core and rods and the biopsies showing the peculiar features, presented areas of myofibrillar disorganization ranging from few sarcomeres to more than 50 sarcomeres of variable width sometimes occupying almost the entire muscle fiber. Areas of disorganization contained variable degree of osmophilic dense filamentous material deposition (possibly corresponding to granular material by optic microscopy) and disorganized thickened z-line fragments. WB analysis on muscle biopsies revealed a constant reduction of RYR1. The percentage of reduction seems to be more pronounced in more severe clinical cases and in patients showing the peculiar morphological phenotype compared to isolated type1 prevalence/uniformity.

http://dx.doi.org/10.1016/j.nmd.2018.06.077

P.50

Loss of FKBP12-RYR1 binding *ex vivo* is a post-translational modification consistently evident across diverse ryanodine receptor 1-related myopathies

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Ryanodine receptor 1-related congenital myopathies (RYR1-RM) are heterogenous, rare, slowly-progressive neuromuscular disorders for which there is no FDA-approved therapy. Estimated to affect 1:90,000 children in the US, causative *RYR1* variants lead to dysfunctional RYR1-mediated $Ca2^{+}$ release, elevated oxidative stress and deleterious post-translational modifications. RYR1 activity is modulated by several interacting molecules, including FKBP12 which binds to RYR1 at the cytosolic shell (4:1 ratio) and stabilizes the channel in the closed state. Clinically, RYR1-RM manifest with a diverse symptomatology ranging from delayed motor milestones, contractures, and scoliosis to ophthalmoplegia and respiratory insufficiency. This pilot study assessed RyR1 post-translational modifications, ex vivo, using skeletal muscle tissue obtained from a genetically and clinically diverse group of RYR1-RM affected individuals that participated in the first natural history study and clinical trial of the disease. Male and female RYR1-RM affected individuals (n= 4 and 6 respectively, mean ± SD age, 38.4 ± 11.0 years) underwent skeletal muscle biopsies. Tissue was analyzed for RYR1-FKBP12 binding (co-immunoprecipitation), channel oxidation (DNP assay), single channel activity (isolated RyR1), and $Ca2^{+}$ leak (skeletal muscle microsomes). Variants (n= 15) were identified within the *RYR1* coding region of the above-mentioned participants and affected both the RYR1 cytosolic shell (residues 1-3613; n= 8) and channel and activation core (residues 3614-5037; n= 7). Regardless of affected RyR1 domain, laboratory analyses revealed decreased RYR1-FKBP12 binding (<25% of control), as well as increased RyR1 oxidation, channel activity and $Ca2^{+}$ leak compared to control. RyR1 channel destabilization may therefore represent a common pathophysiological pathway among RYR1-RM affected individuals. Overall, these results strengthen the rationale for developing therapeutics that target this pathomechanism.

http://dx.doi.org/10.1016/j.nmd.2018.06.078

P.51

Familial variation in phenotype in RYR1-related myalgia-rhabdomyolysis syndrome

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Lately, a syndrome with myalgia and rhabdomyolysis and variants in the ryanodine receptor 1 gene (*RYR1*) has been described. Index patients typically present with rhabdomyolysis induced by exercise, however, we and others have observed pronounced variability of symptoms among index patients with different variants in *RYR1*. *RYR1* is a large gene and many different variants have been related to the myalgia-rhabdomyolysis syndrome. Some of these variants have a surprisingly high allele frequency in the background population. The question therefore arises how *RYR1* variant carrier status manifests itself in family members of symptomatic carriers. We included symptomatic index persons and family members heterozygous for the same *RYR1* variant, in a cross-sectional study. Participants were interviewed and examined clinically with focus on muscle strength and muscle bulk. In addition, a whole-body T1 MRI of muscles was performed. The study is ongoing including additional families. At present, 11 individuals from 5 different families have been evaluated. Three additional families with 7 members are in process of being included. Preliminary results show that family members are typically less affected than index persons. The index person was often the most physically active in the family, and 2 completely asymptomatic carriers were elderly, physically inactive women. Moreover, 2 additional family members, a sister and a father, had no pain, but displayed muscle hypertrophy. The remaining 2 family members had symptoms of myalgia mostly induced by exercise. The results suggest that penetrance of the *RYR1*-related myalgia-rhabdomyolysis syndrome is incomplete probably partly depending on level of physical activity.

http://dx.doi.org/10.1016/j.nmd.2018.06.079

P.52

Cores and cytoplasmic bodies in a patient with asymptomatic hyperCKemia caused by a *RYR1* p.Arg163Cys mutation

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Mutations in *RYR1* are associated with a wide spectrum of clinical muscle disorders, ranging from early-onset congenital myopathies, to late-onset axial myopathy, malignant hyperthermia susceptibility trait, exceptional myalgia and rhabdomyolysis and a rare bleeding disorder. The morphological changes on muscle biopsy vary from central cores to multi-minicores, central nuclei with or without myofibrillar disorganization and congenital fiber type disproportion. CK levels are usually normal or slightly elevated. The proband, a 31-years-old man was referred to our institution for evaluation of persistent high CK levels (up 10-fold-increased). He denied weakness or other muscle related symptoms. His mother had CK levels twice the upper level, and had been diagnosed with fibromyalgia. Proband clinical examination revealed mild bilateral eyelid ptosis, high arched palate, mild scoliosis, and mild bilateral aquiles tendon contractures. No clinical episodes of malignant hyperthermia were reported in the family. A muscle biopsy revealed central cores in both type I and II fibres. Under electron microscopy, in addition to core lesions, several fibres contained cytoplasmic bodies. Molecular analysis showed three strong candidate variants: -*RYR1* (NM_000540.2): c.487C>T, p.Arg163Cys located in exon 6 in heterozygous state -*TTN* (NM_001267550.1): c.53206C>T, p.Arg17736* located in exon 277 in heterozygous state -*TTN* (NM_001267550.1): c.77749T>C, p.Tyr25917His located in exon 326 in heterozygous state Based on segregation analysis in the family, the *RYR1* variant was the disease-causing selected mutation. Our observation expands the clinical and morphological features associated with RYR1 mutations. In the era of next generation sequencing, combination of clinical, pathology and genetic data is crucial to achieve an accurate molecular diagnosis.

http://dx.doi.org/10.1016/j.nmd.2018.06.080

P.53

Clinical, genetic and pathological characterization of a wide paediatric cohort of patients with dominant and recessive *RYR1*-related myopathy

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RYR1 gene mutations cause heterogeneous myopathies, including dominantly inherited central core disease (CCD), recessive multi-minicore and centronuclear myopathies, rhabdomyolysis and susceptibility to malignant hyperthermia (MH). RYR1-related myopathy (RRM) is the most common congenital myopathy in the UK, and is characterized by a wide range of clinical presentations. Here we present a retrospective study on a large paediatric cohort of RRM patients regularly seen at the Dubowitz Neuromuscular Centre in London. The cohort includes 49 patients (27 families), with a mean age of 4.5 years when first seen. Twenty/49 patients had dominant (AD) mutations, 29 recessive (AR). All patients present proximal more than distal weakness. 40/48 (83%) patients aged over 2 years achieved independent ambulation and 38/48 (79%) remained ambulant at last follow up. Scoliosis was observed in 18/49 patients (37%). AR patients showed more frequent prenatal and neonatal symptoms (65% vs 37%), respiratory muscle involvement (38% vs 20%) and feeding difficulties (48% vs 15%) compared to the AD group. 8/29 (27%) AR patients required non-invasive ventilation (average

age 4.9 years). Ptosis, opthalmoplegia and facial weakness prevailed in AR patients, with only one AD patient having mild lateral gaze limitation. No patient had documented MH or rhabdomyolysis. Review of muscle biopsies from 31 patients showed CCD pathology and slow fiber predominance in AD patients (8/12). AR patients (19/31) showed more heterogeneous features including a combination of CCD-type or ill-defined cores, minicores, increased internal/central nuclei, slow fibre predominance and fibre size disproportion. Muscle MRI for 12 patients surprisingly evidenced minimal or no changes in 1 AD and 2 AR patients. Further deep phenotypic analysis is currently in progress. This work further expands current knowledge on RRM, and helps clinical practice and development of future therapeutic interventions.

http://dx.doi.org/10.1016/j.nmd.2018.06.081

P.54
Forced and slow vital capacities in RYR1-RM

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The more common symptoms of RYR1-related myopathies (RYR1-RM) include proximal, facial, bulbar, and/or respiratory muscle weakness, hypotonia, scoliosis, and fatigue. In many cases, respiratory muscle weakness results in respiratory insufficiency, which places individuals at risk of early mortality. To gain a better understanding of respiratory function in RYR1-RM, we assessed pulmonary function using forced and slow vital capacities (FVC, SVC) in this population. Thirty-four individuals (> 7 years, ambulatory) with RYR1-RM completed a 6-month natural history study. Participants performed FVC and SVC tests at baseline and 6-months using standard spirometry (MGC Diagnostics, St Paul MN). Descriptive statistics and student's t-tests and were used to assess disease status and progression. FVC and SVC were also compared in liters and percent predicted using the Bland-Altman test. Thirteen participants (38%) had an FVC of <80% predicted. Percent predicted FVC and SVC did not change between baseline (84.5% +3.2, 84% +3.2) and 6-months (83.8% +3.2, 82.9% +3.2). FVC and SVC values were in agreement within participants (p=0.312). Thirteen participants did not achieve 80% of predicted FVC, suggesting respiratory insufficiency may be a common finding. All participants in this study were ambulatory, highlighting the importance of assessing pulmonary function independent of functional status in RYR1-RM. We found no change in FVC or SVC over 6 months, indicating a stable 6-month time course. FVC and SVC values were in strong agreement, suggesting SVC may serve as an alternative measure of vital capacity, especially when muscle weakness prohibits individuals from performing the forced maneuver. Together, these results suggest FVC and/or SVC may be useful outcome measures for clinical trials in RYR1-RM. However, SVC will need to be further validated.

http://dx.doi.org/10.1016/j.nmd.2018.06.082

P.55
Historical perspective and proposal for a unified ryanodine receptor 1-related myopathies nomenclature

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Identification of the skeletal muscle calcium release channel protein, ryanodine receptor-1 (RYR1), in 1988 and causative variations in its gene, *RYR1*, in 1991 led to the association of impaired calcium homeostasis with muscle dysfunction. Ryanodine receptor 1-related congenital myopathies (RYR1-RM) are histopathologically and clinically heterogeneous, rare, slowly-progressive neuromuscular disorders. Estimated to affect 1:90,000 children in the US, causative *RYR1* variants lead to dysfunctional RyR1-mediated Ca2+ release, elevated oxidative stress and deleterious post-translational modifications. Clinically, RYR1-RM affected individuals can present with a diverse symptomatology ranging from delayed motor milestones, contractures, and scoliosis to ophthalmoplegia and respiratory insufficiency. Historically, RYR1-RM were diagnosed and named based on histopathologic features on muscle biopsy, such as central core disease in 1956, core-rod myopathy in 1965, centronuclear myopathy in 1966, congenital fiber type disproportion in 1969, and multi-minicore disease in 1971. These histopathologic features are non-specific and dynamic over time, may vary based on biopsy site, and may not be present when biopsy is performed at an early age. As additional phenotypic subtypes are associated with *RYR1* variations due to advances and availability of genetic testing (Evans myopathy, first described in 1960; King-Denborough syndrome in 1973; exercise-induced rhabdomyolysis in 2000; atypical periodic paralysis with or without myalgia in 2018), the clinical and histopathologic overlap among RYR1-RM diagnostic categories is increasing. With the continuing emergence of new subtypes on the RYR1-RM spectrum and reports of adult-onset phenotypes, nuanced nomenclatures have been reported (RYR1- [related, related congenital, congenital] myopathies). We present historical accounts of the main diagnostic subtypes and propose revisiting the nomenclature of phenotypes with *RYR1* genetic etiology, which, based on clinicopathological overlap, are shades of the same disorder.

http://dx.doi.org/10.1016/j.nmd.2018.06.083

CONGENITAL MYASTHENIC SYNDROMES AND MYASTHENIA

P.56
Clinical manifestation and associated co-morbidities in patients with juvenile-onset myasthenia gravis: a retrospective study

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Juvenile acquired autoimmune myasthenia gravis (JMG) is a rare disorder of childhood. To further characterize this disorder in pediatric population, we conducted a retrospective study of 21 patients with childhood onset (<18 yo) of myasthenia gravis from April of 2008 to April of 2018. Range of ages at the onset of symptoms was between 13 months and 15 years of age. Sixteen patients (76%) had onset before 10 years of age. Fifteen (71%) patients were females. All affected males (29%) had onset of symptoms before 10th birthday. Sixteen patients (76%) had positive anti-AChR Ab titers. Thirteen patients (61%) had generalized presentation with eleven patients (85%) having positive anti-AChR antibody titers. Patients with ocular myasthenia gravis were positive for anti-AChR antibody titer in 63% of the cases. Co-occurrence of other autoimmune disorders was common and consisted of 33% of the patients with five out of seven had generalized MG. Modalities of treatment used in JMG were similar to what is typically utilized in adult-onset myasthenia gravis. Ten patients (48%) underwent thymectomy. Eleven patients (52%) underwent treatment with IVIG and only six patients (29%) underwent plasmapheresis. Choice of treatment was dependent upon severity and chronicity of the disease. None of the patients required mechanical ventilation during exacerbation and there was no mortality. Fifteen patients (71%) received treatment with corticosteroids. All patients with JMG received symptomatic treatment with pyridostigmine. Seven patients who achieved adulthood remain symptomatic due to residual involvement or various degree of disease activity that requires ongoing immunomodulating treatment. Patient with JMG represent a heterogeneous group with various presentations and severities. In general, majority of the patients with JMG will show an improvement and stabilization but not without residual effect compromising their quality of life and function life-long.

http://dx.doi.org/10.1016/j.nmd.2018.06.084

P.57
Clinical features in juvenile myasthenia gravis in an Argentinian cohort

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Juvenile myasthenia gravis (JMG) is an acquired autoimmune condition of the neuromuscular junction, caused by an antibody-mediated attack on the nicotinic acetylcholine receptor (AChR) and in a small minority associated with muscle-specific kinase (MuSK) antibodies. To determine the clinical and evolution related features of JMG in a 240 argentinian pediatric cohort. Cross sectional study of patients with JMG at three argentinian hospital, from January 1993 to January 2018. We included 240 patients by the symptoms, electrophysiology, AChR or MuSK antibody levels and a positive response to pharmacological treatment. We review medical charts in order to get clinical features from the onset symptoms, presence of antibody. Patients were classified by the MGF scale and compared by clinical features into the prepubertal and pubertal/postpubertal groups. Patients were followed for at least 3 years in order to know the final classification. We included 240 patients, 47% prepubertal, woman 1.85:1 (in prepubertal 1.09:1 and postpubertal 2.28:1), with age mean 7.2 (range 11 months to 17 years old). The onset symptoms were ptosis 83%, ocular symptoms 64% (43% generalized symptoms at 2 years follow-up), 30% had bulbar symptoms and y 12.5% had ventilatory compromised. The 22% (47% en prepubertal) ocular myasthenia gravis 7% had myasthenia crisis. In 78% of our cohort had AChR antibody (61% in prepubertal and 93% in postpubertal), 0.8% anti-Musk and 21% double-seronegative. We saw an stable-remission in 39 % (spontaneously 17%, 57% prepubertal and 29% were postpubertal). Minimal symptoms in 37%, pharmacological remission 19% and 13% remains symptomatic. This paper allow us to know abouts the clinical features, evolution and treatment response of the largest cohort described in Argentina. This encourage us to do a multicenter prospective studies in order to clarify this disease in children and to evaluate the new therapies.

http://dx.doi.org/10.1016/j.nmd.2018.06.085

P.58

Myasthenia gravis anti-MuSK (MuSK-MG): therapeutic experience in 27 patients

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In the first series of MuSK-MG, in addition to a more severe clinical picture with respiratory crises, female predominance and early onset, the lack of response to anticholinesterase drugs and the need for additional aggressive immunosuppression was the most common scenario. This concept was dramatically modified with the use of Rituximab. We present our experience in the treatment of 27 patients with Myasthenia Gravis anti-MuSK. We evaluated the treatments received, and the therapeutic response according to clinical and post-interventional status (PIS) of the Myasthenia Gravis Foundation of America (MGFA) at 6, 12, 24 months and current in a cohort of Musk-MG patient. 27 patients, 20 women (74.1%) and 7 men (25.9%), Mean age onset: 45 ± 16 years (22-76a) and average age at diagnosis 48 ± 16 years (24-77a). Mean time evolution: average 61 ± 46 months (10-192). Initial MGFA: 17 IIa (63%), 9 I (33.3%), 1 V (3.7%), Maximum MGFA: 9 IIb (33.6%), 8 IIIb (28.5%), 5 IVb (18.5%), 5 V (18.5%) They received the following treatments: pyridostigmine, 12 patients (46.2%), steroids, 26 patients (96.3%), azathioprine, 15 patients (55.5%), rituximab, 6 patients (22.2%). The current PIS is: 2 patients (7.4%) PR (Pharmacological Remission), 4 patients (16.7%) CSR (Complete Remission Stable), 3 patients (12.5%) MM (Minimum Manifestations), 5 patients (20.8%) U (without changes), 8 patients (33.3%) I (improvement), 2 patients (8.3%) W (worsening). Our findings are similar with what has been described in the literature. The MG-MuSK is controllable in the medium and long term with conventional therapy, only 8.3% of our patients worsened their clinical picture. The initial stage of the disease is the most unstable and severe where an aggressive strategy and the use of rituximab is recommended.

http://dx.doi.org/10.1016/j.nmd.2018.06.086

P.59

Ocular vestibular evoked myogenic potentials in myasthenia gravis

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Myasthenia gravis (MG) is a neuromuscular disease characterized by fatigability and fluctuating muscle weakness that predominantly involves ocular muscles. The aim of the current study is to study the diagnostic value of the oVEMP test for the diagnosis of MG. oVEMPs were elicited by delivering a vibration to the forehead with a handheld mini-shaker, resulting in bilateral vestibular stimulation via bone-conduction. The oVEMP was recorded by electrodes below the eyes measuring the activity of the inferior oblique muscles. We performed 40 repetitive stimulation trains of 10 stimuli each at 20 Hz and averaged the measurements. Signals were analyzed for decrement using Matlab. We included 38 acetylcholine receptor antibody positive (AChR) MG patients, 10 seronegative MG (SNMG) patients and 11 healthy controls. In both AChR MG and SNMG patients, oVEMP decrement was higher than in healthy controls (20.9% ± 6.0; p=0.01, 25.3% ± 6.5; p=0.04 and -1.8 ± 3.1, respectively). At a cut-off value of 9.5% decrement, the sensitivity of the oVEMP test was 71% and the specificity was 100%. Pure ocular AChR MG patients (n=9) showed a non-significant trend towards a higher decrement than generalized AChR MG patients (n=23) (33.5% ± 8.7 and 13.9% ± 9.0, respectively; p=0.13). Time between the last administration of acetylcholinesterase inhibitors and the oVEMP test showed a trend towards correlation with decrement: every additional hour was accompanied by an increase in decrement of ±5% (p=0.17). Our data show that the oVEMP test could be a sensitive and objective tool in the diagnosis of MG, notably also for SNMG and ocular MG patients. Compared to repetitive nerve stimulation and single-fiber EMG, the test is not painful and examines neuromuscular transmission in the most commonly affected muscles. In contrast to a neostigmine test or ice test, the fully automated analysis yields quantitative data.

http://dx.doi.org/10.1016/j.nmd.2018.06.087

P.60

Respiratory dysfunction in childhood myasthenia

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Prevalence of respiratory dysfunction in pediatric myasthenia is unknown. The only available reports are from the few published pediatric series describing respiratory failure associated with myasthenic crisis. In a recent survey of 52 Canadian patients published in Pediatrics in 2013, two patients with myasthenia developed respiratory failure and another four reported respiratory dysfunction. This current two years long prospective study reports data obtained from patients with pediatric myasthenia at the Hospital for Sick Children in Toronto. Eleven children, ages 3- 18 years with pediatric myasthenia underwent multiple respiratory function tests. They included PFTs, MPI, MEP, SNIP and FVC. These children also underwent sleep study with polysomnographic testing. Obstructive sleep apnea with abnormal Apnea Hypopnea Index was diagnosed in 2 children. One of these two children has juvenile ocular MG with mild to moderate obstructive sleep apnea. The second child has congenital myasthenic syndrome with mild obstructive sleep apnea. CPAP therapy was initiated in both patients. In summary, obstructive sleep apnea rate is higher in children with pediatric myasthenia than in general pediatric population (18% in our study vs. 2-3% reported in general population). Early diagnosis and management of sleep apnea may have an important impact on child's health and quality of life. It remains to be seen, whether these multiple pulmonary tests could identify children who may be at risk for myasthenic crisis.

http://dx.doi.org/10.1016/j.nmd.2018.06.088

P.61

Pembrolizumab induced myasthenia gravis and necrotizing myopathy with severe respiratory failure

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Immune checkpoint molecules are potent regulators of immunologic homeostasis that prevent the development of autoimmunity while maintaining self-tolerance. These drugs are used as immunotherapy in the treatment of melanoma and different types of refractory cancer and can trigger various autoimmune complications including myositis and myasthenia gravis. We report a case of generalized myasthenia gravis and necrotizing myopathy induced by pembrolizumab. We describe a 71-year-old man with metastasic melanoma who started with MG symptoms after de second infusion of pembrolizumab and then developed severe bulbar symptoms and respiratory failure. He was AchR positive and had hyperCKemia. Muscle biopsy showed necrosis and mild inflammation. The patient was treated with high dose of steroids and IvIG and died due worsening of his respiratory status Myasthenia gravis should be considered when weakness, diplopia or bulbar symptoms are seen after treatment with immune checkpoint inhibitors, and additional studies are needed to characterize association with hyperCKemia and necrotizing myopathy association.

http://dx.doi.org/10.1016/j.nmd.2018.06.089

P.62

A case of clinically apparent myasthenia gravis after resection of non-myasthenic thymic cyst

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A 38-year-old woman was referred to our hospital for an incidental thymic cyst. The chest CT demonstrated a 7cm sized cystic and mass lesion in the anterior mediastinum. She had no symptoms of myasthenia gravis(MG). The tumor was completely resected by thymectomy. Histological examination of the tumor identified it as a thymic cyst with fibrous tissue, cystic structure, cholesterol clefts, calcification, necrotic material, and chronic inflammatory lymphohistiocytic infiltrate. Two months after the surgery, she experienced post-thymectomy generalized MG. Acetylcholine receptor antibody (AchR-Ab) was increased and repetitive nerve stimulation test was positive. Her symptoms improved with anti-cholinesterase, prednisolone and azathioprine therapy. The few reported cases of myasthenia gravis after resection of non-myasthenic thymic cyst were reviewed. Also, preoperative factors associated with post-thymectomy myasthenia gravis were also reviewed.

http://dx.doi.org/10.1016/j.nmd.2018.06.090

P.63

Myasthenia gravis like syndrome after botulinum toxin type A injections for calf reduction

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Botulinum toxin type A (BTA) is widely used for both medical treatment and cosmetic purposes. Botulinum toxin type A is a potent neurotoxin and produced by the anaerobic bacterium Clostridium botulinum: It paralyzes the injected muscle by inhibiting acetylcholine release from synapses of neuromuscular junctions and consequently, a dose dependent, reversible denervation develops in muscles. With increasing numbers of people receiving cosmetic botulinum toxin, we should consider the side effects of botulinum toxin type A carefully. We herein report a case of progressive dysphagia after botulinum toxin injection at both the gastrocnemius and soleus muscles.Case: 26 year old woman presented with progressive generalized weakness and dysphagia. The patient had injected BTA into her both calves for cosmetic purposes. The patient also showed ptosis, difficulty chewing. Other neurologic examination findings, including those of the physical examination, brain MRI, and Jolly's test, were normal but nerve conduction system shows neurogenic denervation potential in right medial gastrocnemius muscle. As time had passed by, her symptoms were improved without recurrence. We found only one report of cosmetic botulinum toxin mimicking myasthenia gravis. With increasing numbers of people receiving cosmetic botulinum toxin, an increasing elderly population, and increasing healthcare costs, and because cosmetic botulinum toxin is not regarded as medication by many consumers, it is important to inquire about its use in patients seen with recent ptosis or ophthalmoplegia. Such findings can mimic Myasthenia gravis and provoke expensive serology and invasive tests such as electromyography.

http://dx.doi.org/10.1016/j.nmd.2018.06.091

P.64

Living with myasthenia gravis

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Prevalence of depression and anxiety was observed in patients with myasthenia gravis (MG) as an effect of the unpredictable progression of the disease. Increase knowledge about the psychological and psychopathological disorders in patients with MG. We focused on the analysis of the psychological assessment realized at a point before randomization of patients included in the MGEX Study. Qualitative and quantitative methods: self-report questionnaires to evaluate: anxiety (STAI A-B), depression (Beck depression inventory, BDI-13), psychiatric disorders (MINI, French Version 5.0.0), self-esteem (Self- esteem inventory scale, SEI), quality of life with a MG-specific scale (MGQOL-15-F). Qualitative assessment, conducted by trained clinical psychologists, included: a semi-structured recorded interview to explore the psychological impact of MG on patients. We asked patients to draw themselves to explore self-body image. We assessed n= 42 patients (40 women and 2 men), mean age was 44.6 years [28;70]. The patients' mean score of MGQOL-15-F was 21,9 [5-44]. Psychopathological assessment shows that 30.9% of patients suffer from moderate to high trait anxiety (STAI). Depression was frequent: 38% scored low depression, 26.1% moderate depression, and 9.5% severe depression (BECK). The assessment of psychiatric disorders (MINI) showed disorders such as agoraphobia (23.8%), major depressive episode (16.6%) and dysthymia (11.9%). The majority of patients (97%) scored very low levels of self-esteem, the lowest levels being observed regarding social and professional lives. The interview and the self-portrait show that MG disturbs body image related to inability to maintain an ordinary lifestyle, social role, and responsibilities in professional life. Despite medical knowledge patients have "personal theories" about the origin, the fluctuations and flares of the disease. If rest was perceived as a way of improvement, it appears that "lying down" revives feelings of guilt and shame. The tendency to stay active and to overcome physical signs of fatigue is a way to cope with MG. Engaging in movement despite fatigue can be a way of feeling alive, a kind of defense against anxiety faced with signs of the disease. MGEX Study will be a way of knowing if physical exercise improves the psychological state of MG patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.092

P.65

Muscular pathological features in Lambert-Eaton myasthenic syndrome

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Lambert-Eaton myasthenic syndrome (LEMS) is an autoimmune-mediated disorder of neuromuscular transmission. Voltage-gated calcium channel antibodies (VGCC-Ab) impair calcium influx and acetylcholine

release at motor nerve terminals, resulting in the failure of neuromuscular transmission. Patients present with skeletal muscle fluctuating weakness and paralysis in the clinical. Due to LEMS is often misdiagnosed as a peripheral nerve disease or a myopathy, so electromyography (EMG) and muscle biopsy are necessary. The objective of this study was to describe EMG findings and several muscle histology in LEMS. EMG, nerve conduction studies, repetitive nerve EMG showed significantly decreased mean Muscle action potentials (MUP) duration, normal motor and sensory nerve conduction. RNS showed decrease of compound motor action potential (CMAP) amplitude by at least 10% at low-frequency (2-5 Hz) and increased CMAP amplitude by more than 60% at high-frequency (20-50 Hz). Muscle biopsy showed minor evidence of denervation or marked type II fiber atrophy in the patients with longer duration of illness, whereas with shorter duration, there was scattered muscle fiber necrosis. EMG and biopsy abnormalities mimicking myopathy may often be found in patients with LEMS. Rare muscle pathological features associated with LEMS were described.

http://dx.doi.org/10.1016/j.nmd.2018.06.093

P.66

Congenital myasthenic syndromes: how do clinicians face diagnostic complexity and long-term prognosis in 2018?

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CMS diagnosis often remains difficult, due to: 1) age at onset: (a) in neonates, congenital myopathy (CM) is suspected first; (b) if age at onset is > 2 years, seronegative autoimmune MG is hypothesized; 2) clinical expression differing from a common myasthenic syndrome, with atypical features such as (a) atrophy, scoliosis, contractures, prominent permanent muscle weakness overshadowing motor fluctuations, and myogenic pattern shown by electrophysiology (eg: *DOK7*), (b) unresponsiveness to/negative effect of AChE inhibitors (e.g.: *COLQ*); (c) atypical phenotypes initially orientating towards other neuromuscular diseases: LGMD (*GMPPB*), distal myopathy (*AGRN*), Charcot Marie Tooth (*SYT2*); (d) histopathological pattern in favor a congenital or a metabolic myopathy; (e) "hybrid" entities, combining CM features (histopathology and CM gene, e.g.: centronuclear myopathy, DYN2 gene) and CMS characteristics (fatigability and decrement). Long term prognosis is not easy to predict. We retrospectively studied long term prognosis for of a large cohort of patients harboring slow channel, AChR loss, *DOK7, COLQ, RAPSN, MUSK, AGRN, GFPT, SLC5A7* CMS. Different course patterns may occur in a single patient along his/her lifetime (short-term or long-standing episodes of exacerbation may alternate with progressive worsening/improvement). Late-onset deterioration may affect patients with an initially mild disease. Slow channels and DOK7 CMS were particularly prone to worsen in adulthood. Pregnancy is a risk period, whatever gene is involved. Severity and course may differ, even with a similar mutation in the same gene. In conclusion, the clinical approach, based on an extensive knowledge of various phenotypes and tightly linked with an integrated use of molecular genetics and electrophysiology, remains fundamental to achieve CMS diagnosis and to discuss treatment options and prognosis.

http://dx.doi.org/10.1016/j.nmd.2018.06.094

P.67

Congenital myasthenic syndromes due to impaired principal coupling pathway in the ε-subunit of muscle acetylcholine receptor

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Mechanistic analyses of CMS caused by mutations in acetylcholine receptor (AChR) have guided therapy and yielded insights into structure-function relationships. AChR is a Cys-loop receptor formed by two α, and one β, δ and ε subunits surrounding an ion channel whose opening is triggered by agonist binding to α/δ and α/ε binding sites. A principal pathway that transduces agonist binding to channel opening was identified in the α-subunit: an invariant Arg residue (αR209) in the pre-M1 domain couples with three nearby negatively charged residues (αE45, αE175, and αE138) in different loops extending to the ligand binding site. These residues are also present at the equivalent positions in the ε- and δ-subunits, but their contribution to signal transduction has not been investigated. We identified two homozygous mutations in the AChR ε-subunit in one mildly and two severely affected congenital myasthenic syndrome (CMS) patients: εE184K in the β8-β9 linker in one patient and εR218W in the pre-M1 region in two others that correspond to αE175 and to αR209 respectively in the principal pathway of the α-subunit. We found that εR218W reduces the channel gaiting efficiency 338-fold, whereas εE184K reduces channel gaiting efficiency 11-fold. As in the α-subunit, mutant cycle analyses demonstrate strong energetic coupling between εR218 and εE184, and between εR218 and εE45, which is equivalent to αE45 in the β1-β2 linker. We conclude that rapid gating of the AChR channel is achieved not only by coupling between conserved residues within the principal pathway in the α-subunit, but also between corresponding residues in the ε-subunit. Some patients with mutations impairing the principal coupling pathway in the AChR ε-subunit suffer from severe CMS.

http://dx.doi.org/10.1016/j.nmd.2018.06.095

P.68

The p.N88K mutation in the *RAPSN* gene in Brazilian patients with congenital myasthenic syndrome

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The p.N88K *RAPSN* variant is a common variation found in European patients, but not in South Americans. Patients with p.N88K variant in compound heterozygosis with another pathogenic variant might present different phenotypes, seeming that the heteroallelic p.N88K-rapsyn is an important determinant of phenotype. In order to verify the presence of p.N88K in our population, 61 Brazilian CMS patients were tested for *RAPSN* p.N88K (Sanger sequencing). Three patients, 5%, were shown to harbor the p.N88K mutation, two in homozygosis (case 1 and 2) and one in compound heterozygosis (case 3) with the previously reported pathogenic variant p.V156M. Case 1) 10-year-old boy, with delayed motor milestones and high arched palate, presented from the first months of life fluctuating symptoms, which have partially improved with pyridostigmine. Symptoms included ocular movements impairment, ptosis, dysphagia and dysarthria, but no episodes of respiratory distress. Case 2) 35-year-old man, with no delayed motor milestones nor respiratory symptoms, presented fluctuating symptoms from age of 6 months, which have partially improved with pyridostigmine. Symptoms included ocular movements impairment, ptosis and proximal limb weakness. Case 3) 15-year-old girl with ptosis, neonatal hypotonia, breast feeding difficulties, high arched palate, delayed motor milestones, and repetitive episodes of respiratory failure since birth. Symptoms were fluctuating, but no response to pyridostigmine was seen. She became asymptomatic after adolescence and last episode of respiratory failure occurred at age of 5 years. The last case (case 3) is an unique presentation of a combination of *RAPSN* variants already reported a few times. This raises the possibility that factors other than the second variant of a p-N88K-rapsyn heteroallelic have influence in the phenotype of compound heterozygous patients. Moreover, our data suggest that *RAPSN* patients are under diagnosed in South Americans.

http://dx.doi.org/10.1016/j.nmd.2018.06.096

P.69

New *AGRN* mutations in a patient with limb-girdle congenital myasthenic syndrome

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Limb-girdle congenital myasthenic syndromes (LG-CMS) are a group of genetic disorders of the neuromuscular junction that have already been associated with mutations in 10 different genes. Our patient is a 17 years-old young woman from Polish origin who was referred to the neurology clinic at the age of 8 for walking and running difficulties. Walking was acquired between the age of 18 and 24 months. She always had difficulties for running and her walking perimeter was reduced to a few hundreds of meters. Her examination disclosed shoulder and pelvic girdle weakness. Gowers sign was positive. She had no ptosis nor ophtalmoparesis. Lower limbs were slightly amyotrophic both at the proximal and distal levels. Speech and swallowing were normal. CK were normal. Muscle biopsy was normal. Repetitive nerve stimulation at 2 Hz resulted in a decrement in many muscle groups. Anti-AChR and anti-MuSK antibodies were negative. Sequencing of the *DOK7* and the *COLQ* genes disclosed no mutation. A trial with Salbutamol was beneficial with an improvement in the walking perimeter. Exome sequencing disclosed two variants in *AGRN* gene encoding for agrin: one missense variant c.5356G>A (p.Gly1786Ser) and one inframe deletion c.5387_5389delGCC (p.Arg1796del). Both residues are very conserved residues located in the LG2 domain of agrin in which mutations have previously been associated with CMS. Both mutations are absent in 1KG, ExAC and Gnomad databases. The p.Arg1796del but not p.Gly1786Ser mutation was present in the mother. DNA from the father was not available. *AGRN* mutations are a rare cause of LG-CMS that usually respond well to ephedrine and salbutamol.

http://dx.doi.org/10.1016/j.nmd.2018.06.097

P.70

New homozygous mutation in *DPAGT1* gene leading to LG-CMS with tubular aggregates

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We describe the case of a 13-year-old-girl presenting with a limb-girdle congenital myasthenic syndrome (LG-CMS) due to a new homozygous missense mutation in *DPAGT1*. The patient from Guadeloupe was born to consanguineous parents as they share a great-grandmother. She was able to stay sit at 7 months and walked aided at 16 months. She had speech delay with first words at the age of 27 months. At clinical examination at the age of 10, she presented with axial and shoulder girdle muscle weakness, and abduction of the arms was limited to 45. Her face was poorly expressive without deficit of cranial nerves. She had mild intellectual disability. CPK were normal. Muscle biopsy at 10 years revealed tubular aggregates leading to the diagnosis of congenital myopathy. At the age of 13, EMG showed myasthenic decrement, and muscle MRI revealed global hypotrophy of axial and appendicular musculature with fatty infiltration of legs and glutei muscle. Exome sequencing identified a novel homozygous missense mutation in *DPAGT1* (c.1133A>T; p.Asn378Ile). Pyridostigmine treatment was introduced with a good response. *DPAGT1* encodes for UDP-N-acetylglucosamine-dolichyl-phosphate N-acetylglucosaminephosphotransferase, an essential enzyme that catalyses the first step of N-glycosylation, leading to hypoglycosylation and dysfunction of the Ach receptor. It was first identified as a pathogen mutation leading to LG-CMS presenting with fatigable weakness spares ocular and facial muscle. Tubular aggregates and cognitive impairment association have been described in some *DPAGT1* cases. Tubular aggregates are often seen in congenital myopathies and *DPAGT1*, *GFPT1* or *ALG2*-related congenital myasthenic syndrome. While these three mutations bring about similar phenotypes and response to treatment, no patients with *GFPT1* and *ALG2* mutations have been reported with learning disability or mental retardation so far. This could help us orientate the diagnosis. In conclusion, our case broadens the genetic spectrum of CMS resulting from *DPAGT1* mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.098

P.71

Unexpected findings of congenital myasthenic syndromes by NGS testing using an extended gene panel on neuromuscular patients in Norway

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Neuromuscular disorders (NMDs) contain a broad group of disorders with overlapping symptoms and is therefore difficult to differentiate clinically. A subgroup is a plethora of rare and different congenital myasthenic syndromes (CMS) with different inheritance patterns, severity and possible treatments. Since May 2017, we have offered an expanded gene panel based on Next-generation Sequencing (NGS) to patients with NMDs, including CMS. We performed a NGS-analysis with a gene list of 328 genes on almost 150 patients where standard "gene by gene testing" had not yielded a diagnosis. NGS was performed using Illumina TruSight One Sequencing panel (4813 genes) and run on an Illumina NextSeq 500 Desktop Sequencer. Analyses were done using Illumina BaseSpace BWA Enrichment Workflow and annotation, filtration and variant curation were done using Cartagenia Bench and Alamut Vision. Of the aprx. 150 patients tested by the extended panel, we found three patients with definite CMS based on genetic results of probable and possible pathogenic variants, as well as response to treatments directed by these results. A newborn girl with severe neonatal onset suspected of severe anterior horn disease, was compound heterozygous for variants in *CHRNA1*. A 15-year-old boy thought to have congenital myopathy from a few months of age, had two alterations in *DOK7*. The third, a newborn boy with severe onset, was compound heterozygous for two alterations in *CHRND*. A fourth patient carried two alterations in *CHRNE*, and it remains to be seen whether they are of clinical significance. An extended gene panel designed for NMDs including CMS, resulted in some surprising findings with therapeutic potential.

http://dx.doi.org/10.1016/j.nmd.2018.06.099

P.72

Clinical features of congenital myasthenic syndrome due to mutations in *COL13A1*

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COL13A1 is a membrane protein expressed at the human neuromuscular junction and cleaved via ectodomain shedding into a soluble form that is part of the synaptic basal lamina. In recent years, we have identified that mutations in *COL13A1* underlay a novel subtype of congenital myasthenic syndrome highlighting the importance of collagen XIII in the muscle endplate cytoarchitecture and neurotransmission, and the crucial role of extra-cellular matrix proteins, other than those in the agrin pathway, in the formation and maintenance of the synapse. Here we review 7 patients with *COL13A1* mutations from 6 different kinships in order to identify the associated clinical, neurophysiological, pathological, and genetic features. A total of 6 different mutations were identified, including the first case homozygous for a missense variant. The results showed that age at presentation was variable and main clinical features included respiratory and feeding difficulties, facial dysmorphism, and ptosis with limited fatiguabilty but normal eye movements. Neurophysiological studies showed impaired neuromuscular transmission in all cases. There was no beneficial response to anticholinesterase medication but

patients did improve on β2-adrenergic agonists consistent with the fact that *COL13A1* mutations affect the maturation and maintenance of the synaptic structure. Treatment with 3,4-Diaminopyridine was also beneficial in keeping with the importance of COL13A1 for the integrity of the presynaptic terminal. This study will facilitate the recognition of this genetic disorder, which can be treated pharmacologically.

http://dx.doi.org/10.1016/j.nmd.2018.06.100

P.73

Characterization of an Indian congenital myasthenic syndrome cohort by whole exome sequencing

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Congenital myasthenic syndromes (CMS) are caused by mutations in genes coding for proteins involved in the maintenance of the neuromuscular junction (NMJ). The patients can be effectively treated and prognosis can be improved when the precise genetic cause is known. In addition, the frequency of the different CMS-causing genes varies with ethnic and geographic origin. There are only few reports from India describing the occurrence of *DOK7*, *RAPSN* and *COLQ* mutations based on selective or limited genetic testing, but the prevalence of various gene mutations in the Indian CMS population is unknown, hence, limiting the effective gene screening and thus, prognosis and access to treatments. DNA from 40 genetically undiagnosed CMS families (total of 87 samples) were subjected to whole exome sequencing (WES). Of those eight families were known to be consanguineous, and majority of them had recessive inheritance pattern.WES was performed using Illumina exome capture (38 Mb target). Data analysis was carried out on the Seqr Genome Analysis Platform. Standard filtering criteria were moderate to high VEP (variant effect predictor), MAF of 0.01(1%) and CADD >20.We identified four *GFPT1*, four *DPAGT1*, three *COLQ*, two *MUSK*, one CHRND and one *SLC25A1* variants that we consider as likely disease-causing. All the variants were highly pathogenic and majority of variants were absent in the control population. The overall solved rate after initial screening for known CMS genes was 37.5% cases (15 out of 40). Interestingly, there was occurrence of rare forms of CMS in the present cohort, and several recurrent mutations seen in *COLQ*, *MUSK* and *DPAGT1* genes. These mutations might be hotspots or founder mutations in Indian populations. The remaining patients will undergo further analysis for novel candidate genes.

http://dx.doi.org/10.1016/j.nmd.2018.06.101

P.74

Five years of salbutamol treatment in a girl with congenital myasthenic syndrome caused by mutations in *COL13A1*

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The beneficial effect of salbutamol has been demonstrated in an icreasing number of congenital myasthenic syndromes (CMS). We present a 22 year-old girl who presented at birth with signs of CMS. She was born from consanguineous parents, whose two-year-old first son had been previously diagnosed with a syndrome of congenital insensitivity to pain with anhidrosis, due to a homozygous mutation in the *NTRK1* gene (c.C2011T, p.R643W). Prenatal screening showed that the female fetus carried the mutation in heterozygosity. The patient presented at birth with hypotonia, ptosis, severe respiratory insufficiency and swallowing dysfunction, that required tracheostomy and gastrostomy. Physical examination evidenced dysmorphic features including retrognathia, high-arched palate, and pectus carinatum. EMG identified a myasthenic pattern of muscle activation and treatment was started with piridostigmine and 3,4-diaminopyridine with some improvement. Tracheostomy could be removed at 4 years of age and switched to non-invasive ventilation. During the following years, the patient presented severe episodes of acute respiratory insufficiency that required multiple hospitalizations. Extensive genetic analysis failed to identify the cause of the CMS. Five years ago, treatment was started with oral salbutamol and the patient presented a clear improvement in respiratory funtion and the respiratory crisis completely dissapear. Sequencing of the *COL13A1* gene identified a homozygous mutation c.648C>G (p.Tyr216*). Even without diagnosis, treatment with salbutamol could be worth trying when other therapies were unsuccessful.

http://dx.doi.org/10.1016/j.nmd.2018.06.102

P.75

Development of a home based assessment tool for monitoring fluctuations in symptoms in the myasthenic population

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Characteristics of myasthenia gravis and congenital myasthenic syndromes include muscle weakness and fatigue which can fluctuate week to week, day to day and typically within the same day. Clinical services provide disease monitoring and medical management but currently no objective assessments are used on a regular basis to monitor fluctuations in symptoms in the home setting. This study aims to develop a home based assessment to enable people with myasthenic syndromes to self-monitor fluctuations in symptoms between clinical appointments. This will allow ongoing and accurate feedback of their physical condition during medical reviews. The home based assessment was developed using a mixed methods approach. Qualitative research was carried out to gain further insight and identify challenges people have to overcome when living with myasthenia. 10 adults and 7 children, between the ages of 5 and 18 years, took part in semi-structured interviews. Following the interviews, recurrent themes were extracted; main themes were physiological difficulties, psychological impact, lifestyle management. Based on these themes, a selection of validated, novel and exploratory assessments and questionnaires were identified that aim to capture specific problems identified within the themes. During routine clinical appointments, 40 adult and 15 child myasthenic participants were recruited and completed these assessments. These observations were analysed and items refined using the Rasch approach to psychometric evaluation. Following Rasch, clinical and practical evaluation, a selection of the items has been translated into an 8 item home assessment tool. Currently 20 adults and 10 children are being recruited to complete the home based assessment. Data will be collected for 6 weeks thorough out the year to enable analysis of seasonal variation. The analysis is ongoing and results will be presented at the conference.

http://dx.doi.org/10.1016/j.nmd.2018.06.103

SMA CLINICAL DATA, OUTCOME MEASURES AND REGISTRIES

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A prospective functional assessment in type 2 spinal muscular atrophy in the Spanish population. Importance of the age on disease progression rate

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Spinal muscular atrophy (SMA) refers to a group of autosomal recessive disorders characterized by degeneration of anterior horn cells in the spinal cord resulting in a progressive muscular weakness and atrophy. Our study is focused on the assessment of clinical course in patients with SMA types.

To characterize the natural history of SMA 2 patients to gain further insight into the clinical course, we conducted a prospective observational cohort study of children and young adults with SMA 2. Patients were evaluated every 6 months over an 18 moth period. Demographic, clinical, and genetic data were collected. Clinical outcome was determined with 3 motor function assesment: Expanded Hammersmith Functional Motor Scale (HFMSE), Egen Klassifikation Scale 2 (EK2) and revised upper limb module (RULM). 58 children with a mean age of 9.6 years (range 2-21.4 years) were included, 36 completed 18 months of evaluation. The mean change of the funtional scales at 18 months was: - 0.5 for the HFMSE, - 0.5 for the EK2, +1.7 for the RULM. The sub-group of patients younger than 6 years of age showed an improvement in the mean change of the assessments: +2.7 for the HFMSE, - 4.5 for the EK2, +6 for the RULM; in contrast, the older patients showed a mean change of - 1.2 for the HFMSE, +0.3 for the EK2, and +0.1 for the RULM. There were no significant changes for any of the outcome measures ($p>0.05$). Our results confirm the slow progression rate of the SMA type 2 patients. Younger patient showed a functional improvement in upper limb functional assessment when compared with the older patients. The best knowledge of the rate of progression in different motor functional scales at specific ages and time periods may be useful to compare the long term effect of the new approved therapies. Long follow-up times are needed to show a clinical and stadistical significant progression in this disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.104

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Two years longitudinal data of the European prospective natural history study of patients with type 2 and 3 spinal muscular atrophy

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Spinal muscular atrophy (SMA) is caused by mutations in the survival motor neuron 1 gene. Clinically, SMA manifests in various ranges of severity including progressive muscle weakness and loss of motor function. SMA types are characterized based on clinical severity. Several therapeutic strategies are currently under clinical investigation and the first drug was approved in 2016. Given the variable clinical phenotype of SMA, it is essential to determine the best outcome measures and identify prognostic factors to inform clinical trial design. We set up a prospective multicenter study to characterize the disease course of patients with type 2 and type 3 SMA by using a wide range of standardized evaluations. 81 patients aged 2 to 30 years were enrolled and completed the baseline assessments at 9 sites in France, Germany and Belgium between May 2015 and May 2016. 19 patients are non-sitters SMA type 2, 34 patients are sitters type 2, 9 are non-ambulant type 3 and 19 are ambulant type 3. Cross-sectional analysis established that Motor Function Measure (MFM) scores distribution well discriminated SMA types and sitters/ambulant status. Remarkably, most studied outcome measures (pulmonary function and strength tests, compound muscle action potentials, workspace volume, quality of life scales) differentiated the 4 groups and a good correlation was observed with the MFM score. This suggested the strong relationship between studied outcomes, phenotypes and motor function. The objective of the longitudinal data analysis is to evaluate outcome measures changes over time, possible differences of progression between the 4 groups and effect of different variables such as age on SMA progression. The preliminary results on the first 12-months of follow-up showed that the change in the different outcome was not significant on a 1-year period. This confirmed the previously described slow evolution of motor function in patients with SMA type 2 and 3. We describe here the changes over 24 months for 35 patients. The objective of this analysis is to evaluate the variations of the studied outcomes and biomarkers on a longer period, as well as their sensitivity to disease progression. Generated data will help to characterize the spectrum of SMA and to identify clinically meaningful and relevant assessments for future clinical trials, or for reimbursed drug post marketing evaluation

http://dx.doi.org/10.1016/j.nmd.2018.06.105

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Clinical and molecular features of proximal spinal muscle atrophy in Portugal: a multicentre retrospective study

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Proximal spinal muscle atrophy (SMA) is an autosomal recessive disorder caused by deletions or mutations in the *SMN1* gene, being characterized by lower motor neuron degeneration in the brainstem and spinal cord with subsequent weakness and muscle atrophy. We aimed to raise awareness of phenotypic and genotypic features of alive SMA patients in Portugal. A multicentre, retrospective study was performed in Portuguese tertiary centres from January 2015 to December 2017. SMA patients were categorized into four phenotypic groups according to the age of onset and highest motor milestones. From 88 alive SMA patients, 3 (3.41%) were classified as type I; 46 (52.27%) as II; 38 (43.18%) as III and 1 (1.14%) as IV. No gender differences were found between groups ($p=0.18$). Mean age at diagnosis was 6.33±4.50 months (1-12) in SMA type I, 16.09±6.91 months (9-36) in II and 12.42±11.68 years (1-38) in III. All SMA type I patients were on non-invasive ventilation, and no significant differences ($p=0.35$) were found between II (70.59%) and III (59.26%) regarding this aspect. No significant differences ($p=0.31$) were also observed in relation to scoliosis surgery between SMA type II (50%) and III (37.04%). In SMA type III, a relation between age at diagnosis and ambulation loss was not disclosed ($p=0.10$). Homozygous deletions at exons 7 and 8 or exclusively at exon 7 were the genotypes seen in SMA type II (28.13%; 71.88%) and III (40%; 60%), with no differences between them ($p=0.32$). Compound heterozygotes at the *SMN1* locus were only observed in SMA type I (66.67%). Since a new treatment is available (nusinersen) and confirmatory studies of other agents are now under way, there was a need to increase knowledge about SMA population in Portugal. SMA type II was clearly the most common phenotypic group. All SMA type I patients were on non-invasive ventilation as expected, and a uniform distribution were found between II and III groups regarding ventilation and scoliosis surgery.

http://dx.doi.org/10.1016/j.nmd.2018.06.106

P.79

The relationship between function and muscle strength in the upper limb in a cohort of children with spinal muscular atrophy type II and III – a prospective study

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The upper limb (UL) function in SMA patients has been studied using different functional scales and assessment tools but there are limited data on hand function and endurance. The purpose of this study was to determine what are the relationships between UL function and the muscle strength and fatigability of the hand in children with SMA type II and III. Data were collected at one baseline evaluation when 6 girls and 4 boys (mean age 8 years, range 5. 2 – 10. 9), five with SMA II and five with SMA III (3 ambulant)

took part in the study. To evaluate upper limb function we used the validated Revised Upper Limb Module (RULM); to measure hand grip, thumb pinch strength, and hand function and fatigue we tested the dominant side using the Myotools set (MyoGrip, MyoPinch and Moviplate), recently developed to assess upper limb strength and function in neuromuscular patients. The MyoGrip and MyoPinch have previously been reported to have a significant correlation with clinical severity determined by the MFM scale. In our cohort the average Brook functional score was 4.9 (range from 3 to 6). The RULM total score showed a strong correlation with the average of the three best Myotools scores for hand grip and thumb pinch (Pearson 'r' = .894, (95% CI .779 to .974) and .858 (95% CI .720 to .981) respectively) but only "moderate to low" correlation when hand fatigue was measured with the MoviPlate (r = .423, 95% CI -.183 to .960). There was no significant correlation between the MoviPlate and the MyoGrip, or the MyoPinch total scores ('r' = .467; 95% CI.-.329 to .951; and 'r' = .314; 95% CI -.437 to .939). In this ongoing study, we showed for the first time that the RULM score correlates with muscle strength of the hand but not with fatigue. Although these preliminary data indicates a trend towards an association between function and power in the upper limb of SMA children, to support our findings we intend to investigate the longitudinal effect in a bigger SMA cohort.

http://dx.doi.org/10.1016/j.nmd.2018.06.107

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Survival and ventilation among those with type I spinal muscular atrophy: results from the 2017 Cure SMA membership survey

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In 2017, Cure SMA initiated a yearly membership survey. Surveys were completed for 214 unique individuals with type I spinal muscular atrophy (SMA). Most surveys were completed by parents (97.2%), followed by affected individuals (2.3%), and grandparents (0.5%). At the time of the survey, 50.0% of affected individuals were deceased and the median age of living type I individuals was 8.1 years [range:0-52 years]. Factors associated with death or requiring more than 16 hours of ventilation (an event) are described. Individuals missing a birth, diagnosis, or deceased date and those >28 years of age were excluded, for an analysis sample size of 207. T-tests, chi-square tests, and Fisher's exact tests were used to identify factors associated with an event, death or requiring more than 16 hours of ventilation. Those in the event group (n=151; 73.0%) had a median survival age of 14 months. The event group had a younger average age of diagnosis compared to the non-event group (5.7 months vs. 6.1 months). A lower percentage of those in the event group vs. the non-event group reported use of a BiPAP (bilevel positive airway pressure) machine (27.7% vs. 72.3%; p<0.0001). Those in the event group were also less likely to have participated in a clinical trial than those in the non-event group (26.3% vs. 73.7%; p=0.001). Among a subset of participants with a self-reported SMN2 gene copy number, we found those in the event group were more likely than those in the non-event group to have one copy of the SMN2 gene (19.7% vs. 0.0%, p=0.03). This study provides a broad perspective of survival and ventilation among individuals with type I SMA before widespread availability of treatment, among an older and longer-lived cohort than typically described in the literature. Results suggest that BiPAP use and clinical trial participation can have positive impacts for individuals with type I SMA.

http://dx.doi.org/10.1016/j.nmd.2018.06.108

P.81

Anthropometric and nutritional assessment in SMA type II and III

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Spinal muscular atrophy (SMA) is a hereditary neuromuscular disease marked by the progressive weakness and muscle loss, with obesity as well as malnutrition, gastrointestinal dysmotility, and osteoporosis. Many patients exhibit metabolic abnormalities, such as insulin resistance, diabetes and fatty acid oxidation disorder. This observational study consisted of a nutritional and medical history survey of children with SMA type II and III collected between 2008-2015. We evaluated 109 patients, 55% of them were males, which 78% SMAII and 22% SMAIII. Age at time of evaluation with a median 8.5(1.2-19.7) years. Low height for age was present in 31% of the population, significantly more frequent in SMA II (61vs10% P=0.03). According to BMI, 66% of the population presented normal weight,16% underweight,12% overweight and 6% obesity. Finding higher frequency of malnutrition in SMAII and greater presence of overweight and obesity in SMAIII (19vs40%, p<0.00). Nutritional support was required by 10% of the population and in all cases were AME II.Vitamin D supplementation was required by 37% of the population, significantly more frequent in SMAII vs SMAIII (35vs2%, p<0.00). Scoliosis was present in 62% of the population, significantly more frequent in SMAII (71vs31%, p<0.00), and 10% present pathological fractures. Constipation is more common in SMA II (41vs4% P<0.00). According to metabolic disorders, 5% presented hyperglycemia, and 37% present insulin resistance, defined by HOMA-IR, with no differences according to the type of SMA, but significantly more common in overweight and obese patients(0.46±2.2vs.31±1.2; p=0.03). We did not find hypoglycemia. The 18% of the patients presented hypertriglyceridemia and 54% showed low HDL cholesterol, with no difference according to the type of SMA, and without correlation BMI. Low vitamin D plasma levels was present in 70% of the population, more frequent SMAII, without correlation with pathological fractures. We found significantly higher frequency of malnutrition in SMA II and greater presence of overweight and obesity in SMA III. Insulin resistance was more common in overweight and obese patients, regardless the type of SMA. A significant percentage of the population present dyslipidemia, regardless of the type of SMA and BMI.

http://dx.doi.org/10.1016/j.nmd.2018.06.109

P.82

Vitamin D status among patients with spinal muscular atrophy

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Patients with spinal muscular atrophy (SMA) are at risk of poor bone health. Deficiency of vitamin D could place children at risk for osteoporosis and fractures, thus monitoring this micronutrient is essential to the bone health. This study aimed to measure levels of vitamin D in SMA-patients and investigate their association with SMA type, fractures, and supplementation with vitamin D. We conducted a descriptive observational study of the natural history of SMA in Chile between September 2017 and March 2018. Blood serum 25 OH (Vitamin D) was determined in all patients. We collected demographic data and clinical information including SMA type, Body Mass Index (BMI), fractures history and vitamin D supplementation. Vitamin D levels were stratified in: deficient (less than 20 ng/ml), inadequate (20-29.9 ng/ml), low-normal (30-39.9 ng/ml) and optimal (40-80 ng/ml). For statistical analysis, we used frequency and percentage for categorical variables, and calculated median and standard deviation for continuous variables. A p-value <0.05 was considered as statistically significant. We include a total of 60 patients with SMA, adults, and children, with a median age of 14 years old (range 1-53), 58% male, 14 patients SMA type 1 (23%), 23 SMA type 2 (38%) and 23 SMA type 3 (38%). BMI showed a 53% of patients with underweight level. The median Vitamin D levels were 27 (8.8-75.8 ng/ml), 60% of the patients had deficient or inadequate Vitamin D serum level, from them 14% SMA type 1, 42% SMA type 2 and 39% SMA type 3. Only 27 (45%) receive vitamin D supplementation, and these patients had a significantly higher serum level of Vitamin D (median 33.7 vs. 20.3, p = 0.02). History of bone fractures was present in 21% of all patients. This study showed more than half of patients with SMA with deficient levels of vitamin D especially in SMA type 2 and 3. It is necessary and advisable to monitor

this parameter in patients with SMA and provide adequate supplementation to reach normal levels and not contribute to deteriorating further the bone health, known to be at risk in this disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.110

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Longitudinal study of body composition and bone mass in spinal muscular atrophy type 2/3

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We aim to evaluate the pattern of bone mass acquisition and fracture determinants in type 2/3 patients. DXA measurements of total body less head bone mineral density (TB-BMD and Z-score), bone mineral content (TB-BMC), fat mass (FM) and fat free mass (FFM) were obtained in 19 subjects with SMA (10 SMA2, 9 SMA3) and 19 controls, at baseline and every 12 months for 36 months. At baseline, the median age was 9.4 years. All patients underwent anthropometric (HT SDS, BMI SDS) and biochemical bone turnover evaluations. Six subjects (3 SMA2, 3 SMA3) reported fragility fractures. SMA2/3 subjects did not differ in age, HT SDS, BMI SDS, although SMA2 tended to be lower, thinner and with greater muscle atrophy than SMA3 from T0 to T36; controls were significantly higher than both SMA types at all times ($p < 0.0001$). The BMI SDS was reduced over time in SMA2 with the same FMI (fat mass index). TB-BMD (T24 and T36) and TB-BMD Z-score (at all times) were significantly reduced in SMA2 compared to SMA3 ($p < 0.05$) and significantly lower in SMA compared to controls ($p < 0.0001$). BMC was significantly reduced in SMA2 compared to SMA3 ($p < 0.05$) and in both groups compared to controls; in the upper limbs there was a significant reduction compared to controls only in SMA2. There was no significant difference in bone turnover parameters between controls and SMA2/3. DXA parameters did not discriminate between fractured and not fractured SMA patients. However, multiple regression analysis showed that visceral adiposity predicted fractures after correction for lean mass, skeletal dimensions, or the BMD-Z-score (R2 0.466-0.341, $P < 0.05$). SMA2 have a generalized impairment of DXA parameters, although bone mass acquisition is also reduced in SMA3 compared to controls. In SMA patients, body composition and visceral adiposity would appear to be the major determinants of bone fragility.

http://dx.doi.org/10.1016/j.nmd.2018.06.111

P.84

Clinical discordance in spinal muscular atrophy siblings: the exception or the rule?

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder caused by mutations in *SMN1* gene, characterized by degeneration and loss of motor neurons in the anterior horn of the spinal cord. *SMN2*, a homologous copy of *SMN1*, is considered a phenotypic modifier of the disease. However, unrelated SMA patients with the same *SMN2* copy number but different phenotypes and intrafamilial phenotype discordance in haploidentical siblings have been extensively described. The aim of this study was to provide a phenotypic comparison in a series of Argentinean siblings with SMA. Between 2008-2018, we collected information of the follow-up of 14 sibling pairs, according to SMA type, molecular findings, age of loss of independent gait, need of ventilation, spine surgery and motor function scores. In total we evaluated 8 girls and 20 boys, median age of 120 months (36-324). All pairs had 7-8 exon deletions, except one with a deletion in one allele and a point mutation in the other. Differences in best motor function achieved, SMA type were found in 3 families: two families with boys type II and girls type III and another family with a boy type I and his brother type II. Ten sibling pairs had the same SMA type but showed some differences in clinical and functional evolution. Only 1 family (two type I siblings) showed similar phenotype and clinical features. In 6 families the siblings had different genders. Women were found to be stronger than their brothers, except in one case. These initial results suggest that in the context of the same careful follow-up and clinical evaluation, discordance in siblings appears to be most the rule than the exception. Further clinical studies of larger series are needed to confirm our observation and to discover cis or trans modifiers that explain discordance in haploidentical siblings with SMA.

http://dx.doi.org/10.1016/j.nmd.2018.06.112

P.85

Cognitive performance of children with 5q-spinal muscular atrophy: a systematic review

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Children with spinal muscular atrophy present severe weakness, which may impact on hand coordination and speech acquisition. Restricted sensorimotor and verbal interaction can cause cognitive impairment. This study aimed to evaluate the evidence about cognitive outcomes in children with spinal muscular atrophy. This study was registered in the international prospective register of systematic reviews. We performed electronic searches on PUBMED/Medline, Web of Knowledge and Scielo data sources (1992 to 2017) with the descriptors “spinal muscular atrophy” and “cognition”. We analyzed 26 articles and selected nine because they met the eligibility criteria: (1) tested cognitive abilities of children with spinal muscular atrophy; (2) were written in English or Spanish. We classified bias with the Risk of Bias in Non-Randomized Studies of Interventions guidelines and described the design, bias, participants, evaluation protocol, main findings. In three studies, children with spinal muscular atrophy showed normal cognition. Cognitive performance was described as above normal in three studies. Cognitive impairment was found in three studies. Poor cognitive performance was more frequently reported in studies that (1) were recent, (2) included type I children, (3) included visual/ auditory attention and executive function tests. Testing protocols and cognitive domains varied, therefore it was not possible to compare the results by meta-analysis. In conclusion, the severity of motor impairment may be related to the cognitive outcomes: studies that included a higher number/percentage of children with spinal muscular atrophy type I found cognitive impairment. Children with spinal muscle atrophy, mainly the ones with type I, may present attention and executive function impairment. Gold-standard protocols are needed to investigate the cognition of children with spinal muscular atrophy. Further studies should compare the cognitive outcomes of types I to IV.

http://dx.doi.org/10.1016/j.nmd.2018.06.113

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Cognitive assessment in spinal muscular atrophy type 1-2 using eye tracking system

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Spinal muscular atrophy (SMA) is a devastating inherited disorder caused by ubiquitous deficiency in the SMN protein. SMA main feature is the progressive loss of motor activity caused by motor neurons degeneration leading to muscle atrophy. Recent evidence suggests that SMA is a systemic disease. In the brain SMN is expressed in many cell types in addition to motoneurons. Brain morphology changes have been described, and circadian dysregulation,

abnormal fatty acid metabolism have been observed. Symptoms of signs of a systemic disease may likely become increasingly apparent in treated children treated, where neuromuscular symptoms are alleviated and life extended. Literature on cognitive aspects of SMA type 1-2 is poor and divergent. Indeed, physical impairments make usual IQ tests often unusable in many SMA children. Therefore, we developed an eye tracking system (Tobii®) for the assessment of cognitive functions in SMA patients belonging to the severe end of the spectrum. The set of tests contains the following subtests: Matrix subtest of Weschler non-verbal scale of ability for the study of fluid reasoning and perceptual reasoning. Recognition subtest of Weschler non-verbal scale of ability for the study of visuo-spatial memory. Peabody picture vocabulary test for the study of receptive vocabulary (French). The chimeric animal stroop test to study inhibition. Face recognition subtest of NEPSY-II to study face encoding, discrimination and recognition. Picture complement test to study the spatial reasoning. Matching pair test. Fourty children from 2 to 12 years old were enrolled: 10 SMA type 1, 10 SMA type 2, and 20 age and sex matched control patients. The methodology and first results will be presented. At the era of new treatments, in particular for SMA type 1, many questions are opened and could be partially answered by this approach: What is the natural history of cognition in SMA type 1 (and 2)? What is the impact of new treatment? How to organize the environment of SMA type 1 children in order to achieve optimal cognitive development (language, cognition, participation)? The developed protocol aims at validating eye tracking assessment tool for cognitive functions in SMA type 1 and 2. This study will help to adapt the overall management of patients and to evaluate the impact on cognition of future SMA treatments.

http://dx.doi.org/10.1016/j.nmd.2018.06.114

P.87

Use of the ACTIVE-mini for quantifying movement in infants with spinal muscular atrophy

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Clinical trials in the SMA I population could be advanced by using a motor tracking system that could quantify change in movement while minimizing the burden of testing on fragile children with SMA. ACTIVE-mini uses color tracking to quantify movement characteristics of the extremities such as quantity, velocity and complexity. The reliability and validity of the ACTIVE-mini has not been established for children with SMA. The purpose of this study was to establish the reliability and validity of ACTIVE-mini for children with SMA. Two ACTIVE-mini recordings, each lasting two-minutes, were captured at each visit followed by the CHOP INTEND. The subject then returned within 24 hours to seven days for day two of testing following the same procedure. To administer ACTIVE-mini, infants were placed supine on a mat and movements of the arms and legs were recorded by the using the Microsoft Kinect at 12–30 Hz; individualized encouragement was provided to maximize movement across the trial. The CHOP INTEND was performed in the standard order per the manual. Regularized regression analysis on automatically generated motion features was used to assess the validity of ACTIVE-mini by assessing its ability to differentiate movement in healthy controls and children with SMA and to predict the child's CHOP INTEND score. Using complex modeling, ACTIVE-mini differentiated healthy controls from children with SMA. Further, our model on movement characteristics could predict CHOP INTEND scores at high accuracy. Test-retest was good between testing sessions. ACTIVE-mini appears useful in detecting early movement characteristics that quantify change over time and could be an alternative motor outcome measure that can be used for assessing movement in children with SMA. The low cost, ease of administration, system portability, and minimal burden of testing makes ACTIVE-mini a promising outcome measure for children with SMA and other fragile populations.

http://dx.doi.org/10.1016/j.nmd.2018.06.115

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Associations between NMR, electrophysiological, strength and function variables in SMA type 2 and 3

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NatHis-SMA is a prospective multicentre natural history study on spinal muscular atrophy (SMA) type 2 and 3 incorporating a combination of various measurements over 2 years. Among the 81 patients included, 43 patients were aged between 6 and 30 years. Twenty-four patients were SMA Type 2, 9 non-ambulant SMA Type 3 and 10 ambulant SMA Type 3. We present here the analyses on the relationships between skeletal muscle NMR imaging, electrophysiological, strength and function variables on this population of patients during a two-year follow-up. Measurements were performed in the forearm and hand muscles. Fat fraction, cross-sectional area (CSA) and contractile CSA values were determined for the forearm flexor muscles of 11 patients using manually segmented Dixon NMR imaging. Maximum motor response were induced in 38 patients on the anconeus and abductor digiti minimi muscles by maximal stimulation of the radial nerve and the ulnar nerve, respectively. Each compound muscle action potential (CMAP) was characterized by its amplitude and area. Grip and pinch strength were measured in 43 patients using the MyoGrip and MyoPinch dynamometers. Muscle function was assessed in 43 patients using the motor function measure (MFM) from which the dimension on distal motor function was deduced (MFM-D3). Spearman rho or Pearson correlation coefficients were computed between variables depending on monotonic or linear assumption on their relationship. All variables were moderately to strongly correlated to each other. Particularly, strength, CMAP amplitude and contractile CSA were closely associated. The poster will show the changes observed over two years in these variables in the patients. First analyses show that the patients are very slowly progressing. Interestingly, in this first analysis, some variables such as contractile cross-sectional area assessed by NMR or pinch strength are more sensitive to change. This will be confirmed in the subsequent analysis of the full dataset.

http://dx.doi.org/10.1016/j.nmd.2018.06.116

P.89

More than just fun and games: ACTIVE workspace volume video game quantifies meaningful change in function in individuals with spinal muscular atrophy

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This study explored the utility of ACTIVE scaled workspace volume scores to quantify meaningful change in individuals with spinal muscular atrophy (SMA) due to disease progression or treatment. ACTIVE, a 65-second custom designed video game, uses a skeletal tracking algorithm to quantify the volume of space (m3) the player can interact with while reaching in three dimensions to squish spiders or dig for jewels. Sixty-two individuals with SMA type 2 or 3 (age 10.5y +/-5y) and 362 age-matched controls (age 10.7y +/-3.5y) participated. Individuals seen in our clinic (n=37) also completed traditional assessments including the PROMIS self-report of upper extremity function, Hammersmith Functional Motor Scale Expanded (HFMSE), and revised upper limb module (RULM). The remainder were tested at a CureSMA meeting (ACTIVE only n=25). ACTIVE differenti-

ated between patients with varying severity of SMA, as defined by their Brooke level, and from healthy controls (Jonckheere-Terpstra test for trend P<0.0001). ACTIVE significantly correlated with the HFMSE and the RULM (Rho=0.8-0.9, p<0.01). Relevance to patients and families was established by strong correlations to self and parent measures of upper extremity ability (Rho=0.6-0.7, p<0.01). Nine individuals (age 9.4y +/- 4.8y) in this cohort received Spinraza. Responsiveness to change was demonstrated by significant changes pre and post treatment (Median change = 28 pts, Wilcoxon signed rank test p=0.02). Two methods were used to calculate a minimal clinically important difference (MCID). Using the more conservative of the 2 estimates (14.5 pts), all but one Spinraza-treated patient exceeded the MCID, suggesting a robust change not due to random fluctuation. In contrast, no SMA patients in our natural history cohort improved greater than the MCID. Our results validate ACTIVE for use in an SMA cohort and suggest meaningful functional change post-treatment can be readily detected using ACTIVE in individuals with SMA types 2 and 3.

http://dx.doi.org/10.1016/j.nmd.2018.06.117

P.90

The shifting landscape of SMA: development of a new mild mouse model to better understand disease in aging

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Spinal muscular atrophy (SMA) is a devastating neuromuscular disorder characterized by paralysis and muscle weakness and can affect both children and adults. The first FDA approved SMA therapeutic, Spinraza, improves SMA patients' symptoms and motor function. It is expected that increased lifespan will lead to a shift from the severe infantile SMA population to a milder SMA adult population. It is unknown whether such lifespan extension will reveal new, previously unknown defects that could arise with age, as mild mouse models of SMA are currently lacking. We generated a new mouse model, the Smn2B/-;SMN2+/- mice, which present with nearly normal lifespan and very subtle SMA features. We have characterized canonical features of SMA as well as examined non-neuronal organs over the course of an aging study (18 months). The Smn2B/-;SMN2+/- mice are mildly weaker on motor tests and start losing weight at around 12 months of age. Histologically, Smn2B/-;SMN2+/- mice displayed reduced muscle fiber size and increased central nucleation while motor neuron counts seemed spared. Muscle-nerve electrophysiological assessment of the soleus revealed a significant motor neuron/NMJ component as nerve stimulation lead to lower force production than direct muscle stimulation. Interestingly, female mice appear less affected. Many parameters of the twitch and tetanic force production were also altered. Ultrastructural analysis of the sciatic nerve is underway. Thus far, there is no significant impairment in the lymphoid organs, liver and heart, where defects were previously identified in more severe models. Altogether, this study will shed light on future potential obstacles we may face in our changing SMA population. Being proactive in understanding this aspect will ensure timely development of additional therapeutics and ensure sustained quality of life for SMA patients throughout their lifespan.

http://dx.doi.org/10.1016/j.nmd.2018.06.118

P.91

Muscle imaging and function in patients with spinal and bulbar muscular atrophy

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Spinal and bulbar muscular atrophy (SBMA), also called Kennedy disease, is a slowly progressive disease with weakness and atrophy of the bulbar and extremity muscles. Muscle quality and involvement pattern have not been investigated systemically in this patient group. In this study, we investigated phenotypic features, with emphasis on muscle, in 40 patients with SBMA using MRI, stationary dynamometry, questionnaires and functional tests. Patients with a genetically confirmed diagnosis of SBMA were included. MRI was used to describe muscle involvement and quantify muscle fat fractions of arm, back and leg muscles. Muscle strength was assessed with a stationary dynamometer. All patients were evaluated with the SBMA functional rating scale (SBMAFRS) and the 6-minute walk test (6MWT) among others. MRI and muscle strength results were compared with healthy controls. Forty patients with SBMA were included. The muscle fat content was significantly higher in patients with SBMA than in controls: paraspinal fat fraction was 45% in patients *vs* 33% in controls, thigh fat fraction was 36% *vs* 14%, calf fat fraction was 37% vs 15%, upper arm fat fraction was 20% *vs* 8%, and forearm fat fraction was 20% *vs* 9%. The most severely affected muscles were the posterior muscles of both the thigh and calf. Further, the tongue was affected in the majority of patients. Muscle strength was lower in patients compared to controls. Muscle fat content correlated with the corresponding muscle strength. Leg muscle fat content also correlated with SBMAFRS score and 6MWT distance. Our results showed a diffuse muscle involvement pattern in SBMA. Leg muscles were more vulnerable than arm muscles, especially the posterior flexor muscles. The muscle fat contents correlated with muscle function and disease severity.

http://dx.doi.org/10.1016/j.nmd.2018.06.119

P.92

Clinical and molecular characterization of non-5q spinal muscular atrophies

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Spinal muscular atrophies (SMA) are motor neuron disorders classified as 5q-SMA and non-5q-SMA. The first is caused by the absence or alteration of the *SMN1* gene and is considered one of the main hereditary causes of infant morbidity and mortality. Non-5q SMA consist of subtypes of SMA unrelated to *SMN1* mutations. Non-5q SMA shows a great genetic heterogeneity making confirmation of diagnosis very difficult and which is partially solved with the recent appearance of NGS techniques. Our aim was to describe clinical and molecular features of a series of patients with a non-5q diagnosis. We report five patients with clinical and neurophysiological features and, in some cases, biopsy findings consistent with SMA but negative for SMN1 deletions. All patients had clinical signs of anterior horn involvement as muscular atrophy, weakness and areflexia. Specific additional signs were found to orientate the main clinical suspicion of each patient. Two patients had progressive pontocerebellar hypoplasia and *EXOSC3* mutations were confirmed during the first year of life. A third patient developed severe distal weakness at 5 months and diaphragmatic paralysis was observed. SMA with respiratory distress type 1 (SMARD1) was suspected and mutations in *IGHMBP2* confirmed the diagnosis. The remaining two patients had bone abnormalities: one was diagnosed as spondylometaphyseal dysplasia (Kozlowski type) at 2 years and *TRPV4* mutations were found; in the other patient, a hemivertebra was detected and a *DYNCH1H1* mutation also confirmed diagnosis. Patients with clinical and neurophysiological features compatible with SMA and absence of *SMN1* mutations should be considered as non-5q SMA. The study of guiding specific signs helps in the clinical diagnosis and together with molecular studies, are necessary to categorize these patients to offer adequate follow-up, genetic counseling and treatment alternatives.

http://dx.doi.org/10.1016/j.nmd.2018.06.120

P.93

Collaborative data collection by TREAT-NMD registries to support post-marketing surveillance in spinal muscular atrophy

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Spinal muscular atrophy (SMA) is a rare genetic neuromuscular disorder caused by a loss of motor neurons in the spinal cord and the brainstem, leading to muscle weakness and atrophy. The estimated incidence is 1:6,000 to 1:10,000 live births. TREAT-NMD is a neuromuscular network that aims to ensure that the most promising new therapies reach patients as quickly as possible. The TREAT-NMD Global Network of SMA Registries (n=50) collect a common core dataset and are governed by the TREAT-NMD Global Database Oversight Committee (TGDOC). Researchers and industry can request anonymised and aggregate data via the committee, offering a single point of access to this diverse and extensive dataset. The core dataset was established 10 years ago when the main purpose of the registries was clinical trial readiness and recruitment. In the current SMA landscape there is a need for more widespread longitudinal data collection to support future research and post marketing surveillance (PMS) requirements for emerging therapies, and with this in mind TREAT-NMD are reviewing and expanding the core dataset for their SMA Registries. A workshop was held in May 2017 involving clinicians, physiotherapists, registry curators, patient representatives and other stakeholders from across the world, who developed a proposed expanded dataset containing 38 data items. The TREAT-NMD SMA registries are diverse and are not all able nor suitable to collect this level of data, therefore a smaller sub-group of SMA registry sites (n=12) are piloting it for feasibility. Feedback from the pilot sites will be collated and used during a second workshop in June 2018, alongside awareness of and alignment with other SMA data collection initiatives, to make recommendations on (a) the content and structure of the expanded core dataset, and (b) the timescales, costs, and considerations for the full-scale roll-out to all 50 TREAT-NMD SMA Registries. This poster will present the results of this work.

http://dx.doi.org/10.1016/j.nmd.2018.06.121

P.94

Cure SMA membership: findings from the 2018 membership survey

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In February 2017, Cure SMA conducted a membership survey to understand the burden of illness, treatment patterns, and quality of life of those affected with spinal muscular atrophy (SMA). A year later, in March 2018, Cure SMA launched a follow-up survey to learn how experiences with SMA have changed since the FDA approval of nusinersen in December 2016. We will present an overview of the demographic, healthcare and treatment information of individuals with SMA collected in the 2018 survey. Descriptive information about those completing the questionnaire will be provided. Key demographic characteristics of the individuals with SMA will be summarized across all participants and within SMA type, including the age distribution, the percentages who are living and deceased at the time of the survey, and the average diagnostic delay. The use and type of respiratory intervention will be reported. Additionally, the overall percentage of those who report having an SMA-related surgery will be given as well as the most common surgeries by SMA type. The most frequent reason(s) for hospitalization in the last 12 months will be presented overall and by SMA type. For the first time, we will report the percentages of individuals who report being treated with an approved disease modifying therapy (nusinersen), overall and by SMA type. For those not currently being treated with nusinersen, primary self-reported reason(s) for non-treatment will be summarized by SMA type. Findings will highlight the experiences of Cure SMA community members. We will report on the percentage of individuals in the Cure SMA community who are currently being treated with nusinersen and self-reported barriers to treatment. These data can advance the understanding of SMA and the self-reported uptake of available treatments and the use of respiratory interventions in the era of disease modifying therapy.

http://dx.doi.org/10.1016/j.nmd.2018.06.122

P.95

Economic burden of infant-onset (type 1) spinal muscular atrophy: a retrospective claims database analysis

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Spinal muscular atrophy (SMA) is a rare genetic, life-threatening neuromuscular disease. Data on the cost burden of SMA type 1 (SMA1) for U.S. health plans are limited as most studies do not differentiate between SMA types or have consisted of a post-hoc subset based on age at diagnosis. This retrospective analysis estimated the economic burden of SMA1 using QuintilesIMS's PharMetrics Plus Health Plan Claims Database. Infants with ICD-9 codes for SMA ≤1 year old were classified as SMA1 (N=119) and matched (1:1) with a random sample of infants by age, gender, index year, and Charlson Comorbidity Index (CCI). Healthcare resource utilization (HCRU) and costs (pharmacy, outpatient, and inpatient/hospitalization) incurred between February 2011 and November 2016 during the post-index/follow-up period (≥30 days up to 360 days) were compared. Significantly more SMA1 patients (98.32%) received ≥1 pharmacy, outpatient, or in-patient services (54.62%; P<0.0001). Mean per-patient-per-month (PPPM) all-cause HCRU was significantly higher for SMA1 infants: pharmacy (1.43 *vs*. 0.37 prescriptions); outpatient (14.10 *vs*. 2.17 services); and in-patient (0.23 *vs*. 0.003 admissions) (all, P<0.0001). Mean PPPM hospital admissions (0.23 *vs*. 0.003), length of hospital stay (6.93 *vs*. 0.09 days), procedures per admission (1.49 *vs*. 0.03), and readmissions (0.04 vs. 0.00) were also significantly greater for SMA1 infants (all, P<0.0001). Pharmacy, outpatient, and inpatient costs PPPM were significantly greater in SMA1 infants ($371 *vs*. $20; $4,192 *vs*. $232; and $22,500 *vs*. $22, respectively [all, P<0.0001]), resulting in extrapolated all-cause total annual costs of $324,751 (SMA1 cohort) *vs*. $3,294 (matched cohort). The economic burden of SMA1 is substantial; a treatment that alters the early natural course of the disease might result in long-term cost savings.

http://dx.doi.org/10.1016/j.nmd.2018.06.123

P.96

Number needed to treat in spinal muscular atrophy type 1 with AVXS-101 relative to nusinersen

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Spinal muscular atrophy (SMA) is a rare genetic and life-threatening neuromuscular disease. This study assessed the number needed to treat (NNT) to prevent death and use of permanent assisted ventilation and improve motor function with AVXS-101 compared to nusinersen in patients with SMA type 1 (SMA1). Patients diagnosed with SMA1 were treated in clinical trials with AVXS-101 (NCT02122952; study cohort 2; N=12) or nusinersen (NCT02193074; N=80). Trial duration was up to 24 months for AVXS-101 (median = 24.1 months) and up to 13 months for nusinersen (median = 9.2 months). NNT with AVXS-101 compared to nusinersen was assessed for survival and event-free survival (absence of death and use of permanent assisted ventilation) at last visit, and for motor function (increase of ≥4 points in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] score from baseline) at last visit and at a median of 9 months. For the nusinersen trial, CHOP-INTEND score was measured

for patients with ≥6 months of follow-up (N=73). The NNT to prevent one death, one event (death or use of permanent assisted ventilation), or for one patient to improve motor function relative to nusinersen was calculated as the reciprocal of the difference between AVXS-101 and nusinersen in event rates or motor function achievement rates. Patient mean age at first dose was 3.4 (0.9-7.9) and 5.3 (1.7-7.9) months in the AVXS-101 and nusinersen trials. NNT analyses suggests that treating 6.2 patients with AVXS-101 instead of nusinersen would prevent 1 more death by the last visit; treating 2.6 patients with AVXS-101 versus nusinersen would prevent 1 more event; and treating 3.5 patients with AVXS-101 versus nusinersen would allow 1 more patient to improve motor function (at last visit and at a median of 9 months). Efficacy in preventing death and use of permanent assisted ventilation and in improving motor function is much higher with AVXS-101 versus nusinersen.

http://dx.doi.org/10.1016/j.nmd.2018.06.124

P.97

Development of a decision-analytic model for the economic evaluation of newborn screening for spinal muscular atrophy

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Economic considerations are increasingly important to help decision makers to efficiently allocate health care resources. To date, very little information is available on the cost-effectiveness of spinal muscular atrophy (SMA) treatment and newborn screening; yet more and more screening programs are being implemented in the USA and in Europe. The aim of this study is therefore to develop a decision-analytic model to assess the cost-effectiveness of newborn screening and pre-symptomatic treatment of SMA as compared to post-symptomatic treatment. Newborn screening for SMA has started since Marsh 05th in Southern Belgium. We are developing a decision-analytic model in Excel with a lifetime horizon and a societal perspective. This model includes events (such as death, permanent ventilation, etc), transition, utilities, and costs. Data was retrieved from literature reviews, available non-published data from Nurture, and data collected from the European Natural History Study in SMA. We also collected data from the large post symptomatic treated cohort of Liege, Belgium. All such data was acquired in centers applying updated standards of care. The quality of life of patients and parents was included in the analysis, as well as the productivity losses of parents. The model thus estimates the costs and effects (expressed in quality-adjusted life years) of newborn screening and to compare it with a situation where all patients are diagnosed post-symptomatically. Initial data suggests promising results and reveal key factors on the cost-effectiveness of NBS. The model requires adjustment to be fully validated.

http://dx.doi.org/10.1016/j.nmd.2018.06.125

LGMD AUTOSOMAL RESSESSIVE AND DOMINANT

P.98

AAV-mediated gene transfer of FKRP for therapy of LGMD2I

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Dystroglycanopathies constitute a group of genetic diseases caused by defective glycosylation of alpha-dystroglycan α, a membrane glycoprotein involved in the cell/matrix anchoring of muscle fibers. The aDG glycosylation, a very complex process, requires many proteins whose functions are not fully elucidated. In particular, mutations in the *FKRP* gene encoding Fukutin related protein lead to hypoglycosylation of α, resulting in different forms of dystroglycanopathies, among which Limb Girdle Muscular Dystrophy type 2I (LGMD2I). We and others have published the proof of concept of *FKRP* gene transfer using an AAV vector for treating FKRP deficiencies. As the knock-in mouse models used in these studies are not severe enough to evaluate properly the dose-effect of AAV-FKRP administration, we developed a muscle specific FKRP knock-down mouse model. This new mouse model, named HSA-FKRPdel, presents a much more severe phenotype than observed in knock-in mouse. Defects of glycosylation of αDG and of its binding to laminin were observed, as well as histological dystrophic signs as centronucleation and inflammation. Functional evaluation also showed a reduced force of HSA-FKRPdel mice. AAV-*FKRP* was systemically administrated to this new mouse model at different doses. Depending of the dose, positive effects were observed at the molecular, histological and functional levels. Full animal characterization and therapeutic effects will be presented. Development of AAV production at the GMP level is now on going. These data will be included in an IND for AAV-mediated transfer of FKRP in patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.126

P.99

Limb-girdle muscular dystrophy 2Z in a Bulgarian family

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Mutations in *POGLUT1* (protein O-glucosyltransferase 1), an enzyme involved in Notch posttranslational modification and function have been recently identified as causing a new type of limb-girdle muscular dystrophy, known as LGMD2Z. The clinical features of the identified patients encompassed variable clinical onset from 1st to 5th decade, muscle weakness predominantly in the proximal lower limbs, followed by upper limb involvement and wheelchair confinement. We report a Bulgarian family with three affected sisters, homozygous for R98W mutation in *POGLUT1*. They underwent neurological examination, electromyography, measurement of creatine kinase, ventilatory assessment, electrocardiography, echocardiography and muscle muscle magnetic resonance imaging (MRI). The initial complaints in two of them were noticed at the age of 24-25 years, while in the third- at the age of 44 years. The leading symptoms at onset were muscle weakness in the proximal leg muscles with difficulties in climbing stairs and getting up from squatting position. The involvement of the upper limbs was noticed between 6 and 23 years after the lower limb weakness. CK was within normal range in all three affected. The cardiac function seamed spared, mild restrictive respiratory involvement was observed in only one of the sisters. MRI of the legs revealed early fatty replacement of internal regions of thigh muscles and sparing of the external areas. In conclusion *POGLUT1* mutations are associated with late onset AR LGMD with specific MRI pattern of inside-to-outside mode of fatty degeneration in the lower limbs.

http://dx.doi.org/10.1016/j.nmd.2018.06.127

P.100

***BVES* loss-of-function mutations in limb-girdle muscular dystrophy 2X with cardiac conduction disorders**

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BVES encodes for a 360 amino acid protein also known as POPDC1, which is part of the Popeye domain containing (POPDC) family of proteins. POPDC1, POPDC2 and POPDC3 are cAMP-binding transmembrane proteins that are abundantly expressed in striated muscle. A homozygous

missense mutation (p.Ser201Phe) in *BVES* has been identified in three individuals from one single family, the eldest presenting with an overt limb-girdle muscular dystrophy phenotype and all three of them showing an elevated creatine kinase (CK) level and a second-degree atrioventricular (AV) block. The disease was classified as LGMD2X. We performed whole exome sequencing (WES) in a large cohort of patients with unexplained limb-girdle muscular weakness (LGMW) and/or an elevated CK level. Immunohistochemical, Western blotting and mRNA experiments of patients' skeletal muscle tissue were performed to study the pathogenicity of identified loss-of-function (LOF) variants in BVES. We identified 4 individuals from 3 families harboring homozygous LOF variants in *BVES*. Patients showed skeletal muscle and cardiac conduction abnormalities of varying nature and severity, but exhibited at least subclinical signs of both skeletal muscle and cardiac involvement. Identification of LOF mutations in *BVES*, causing an adult-onset skeletal muscle disorder with concomitant cardiac conduction disorders, underlines the role of POPDC family, and POPDC1 in particular, in striated muscle disease. This recessive disorder linked to mutations in *BVES* appears of low prevalence, but is probably underdiagnosed due to its striking phenotypic variability and often subtle yet clinically relevant manifestations, particularly concerning the cardiac involvement.

http://dx.doi.org/10.1016/j.nmd.2018.06.128

P.101

Recurrent rhabdomyolysis and subtle proximal weakness in two female siblings diagnosed with alpha sarcoglycanopathy and a review of the literature

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Rhabdomyolysis is a rare yet important disorder to understand given its potential devastating outcome. Sarcoglycanopathies are limb girdle muscular dystrophies encompassing a broad spectrum of manifestations from very mild to a clinical syndrome indistinguishable from severe dystrophinopathies. We describe the clinical presentation, diagnostic process and the progress of two female siblings presenting with post-exercise muscle cramps, pigmenturia and elevated CK along with minimal proximal weakness and genetically confirmed alpha sarcoglycanopathy (LGMD2D). Diagnosis was made by a targeted massive parallel sequencing panel of neuromuscular genes demonstrating homozygous c.220C>T (p.Arg74Trp) mutations in exon 3 of the *SGCA*. In addition, a systematic literature review was undertaken of the previously described clinical presentations (inclusive of rhabdomyolysis) of alpha sarcoglycanopathy. The siblings described had an unusual LGMD2D presentation of recurrent post-exercise rhabdomyolysis (pseudo-metabolic phenotype) with subtle proximal weakness. A similar pseudo-metabolic presentation in 9 patients has been reported in the literature with either solely or predominant post-exercise symptoms. Sarcoglycanopathies should be considered in the differential diagnosis for children with recurrent post-exercise myalgia and rhabdomyolysis particularly if the metabolic work up is negative. Molecular genetic testing for sarcoglycanopathies is an effective non-invasive alternative to muscle biopsy and immunohistochemical testing. Phenotypic severity in sarcoglycanopathies is highly variable and likely relates to residual protein functions. In addition, the intrafamilial variation of symptoms and the potential compensatory effect of Epsilon sarcoglycan in LGMD2D may suggest the existence of modifiers for this disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.129

P.102

Limb girdle muscular dystrophy type 2A: Divergent features of mitochondrial deficiencies associated with novel calpain-3 mutations

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Limb girdle muscular dystrophy type 2A (LGMD2A) is an autosomal recessive disorder characterized by progressive proximal muscle weakness and wasting. LGMD2A is caused by mutations in the calpain-3 gene that encodes a $Ca2^{+}$-dependent cysteine protease predominantly expressed in the skeletal muscle. Although many important advances have been made, underlying pathological mechanisms have not yet been fully elucidated. Several line of evidence have however clearly indicated the occurrence of mitochondrial abnormalities in mouse models of LGMD2A. Yet, mitochondrial deficiencies were not clearly illustrated in patients harboring calpain-3 pathogenic variants. In the current study we combined histochemical, immunohistochemical, biochemical and ultrastructural analyses in order to have a deeper insight into potential mitochondrial deficiencies in two LGMD2A patients. The diagnosis of LGMD2A in both patients was first suspected on the basis of a typical clinical localization of the muscle weakness, and further confirmed by immunohistochemistry and molecular investigations. Accordingly, two novel homozygous mutations, c.2242C>G (p.Arg748Gly) and c.291C>A (p.Phe97Leu) were identified. Interestingly, c.2242C>G (p.Arg748Gly) mutation was associated with a significant mitochondrial mass depletion in the first patient, while c.291C>A (p.Phe97Leu) mutation was accompanied by a mitochondrial proliferation with ragged red fibers (RRFs), many of which were cytochrome c oxidase (COX) negative myofibers, in the second patient. Results noted with each of the two novel mutations are compared and discussed.

http://dx.doi.org/10.1016/j.nmd.2018.06.130

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A very early onset of calpainopathy (LGMD2A)

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Calpainopathy is one of most commmon form of limb girdle muscle distrophies (LGMD), caused by mutations in *CAPN3* gene. Phenotypic aspects include involvement of the pelvic, scapular and trunk muscles, usually with slow and progressive evolution. Loss of ambulation occurs approximately 10-30 years after the onset of symptoms. We describe a 24 year old female patient with a history of difficulty walking since childhood. Her parents reported muscle hypotonia noticed in first months of life by pediatrician. She just acquired independently walking after 2 years. During childhood and adolescence showed progressive difficulty to walk long distances, climb stairs and never practiced sports. In last years she started to fall frequently, with difficulty getting up from the floor. No family history of similar clinical pictures were reported, but her parents are consaguineous. At physical exam she presented with a waddling gait, hyperlordosis, no scapular winging or weakness in upper limbs, but proeminent proximal weakness in legs and axial muscles (abdominal wall muscles and paravertebral). She had a high CK (1.500 U/L) and muscle MRI revealed fatty replacement with predominant involvement of posterior thigh muscles, and at lower leg a selective involvement of medial gastrocnemius. We found a homozygous mutation of an in frameshift variant described as NM_000070 (*CAPN3*_v001): c.759_761 from *GAA*; (Lys254del), classified as pathogenic in the *CAPN3* (OMIM: 114240). What surprise us in this case of calpainopathy was the age of clinical onset, reported since first months of life. Most series of literature report a range of symptoms onset from 2 to 40 years, with most cases beginning in second decade. In a study of Brazilian population about the occurrence of calpainopathy in children, the age of onset ranged from 3 to 12 years with a median of 9 years.

http://dx.doi.org/10.1016/j.nmd.2018.06.131

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Coalition to Cure Calpain 3: a patient organization committed to treating and ultimately curing limb girdle muscular dystrophy type 2A

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Coalition to Cure Calpain 3 (C3) was founded in 2010 with a mission to fund research and clinical trials relevant to limb girdle muscular dystrophy type2A/calpainopathy (LGMD2A), to support a network of families affected by this disease, and to raise awareness of LGMD2A in the global community. We are governed by a Board of Directors including two LGMD2A patients, a Scientific Advisory Board composed of academic scientists, and a Scientific Director. C3 provides support for promising research focused on understanding pathomechanisms of or finding treatments for LGMD2A. LGMD2A is characterized by proximal muscle weakness. Patients are usually diagnosed before their second decade and experience progressive skeletal muscle wasting in all muscles leading to loss of ambulation approximately 10 years after diagnosis. LGMD2A is caused by mutations in CPN3, the gene which encodes the proteolytic enzyme calpain 3. Despite being the most common subtype of limb girdle muscular dystrophy, the pathophysiology of LGMD2A is still not well understood. Furthermore, the biological function of the calpain 3 enzyme is not entirely clear. C3 has funded research on the basic biology of calpain 3, has supported preclinical studies in LGMD2A models, and has sponsored the generation of tools for use in studying LGMD2A. C3 has also organized two workshops (in the US in 2011 and in the Netherlands in 2013) that have been instrumental in bringing together experts in relevant fields to discuss basic science and clinical information pertaining to LGMD2A, and has a third planned for October 2018. A travel grant program, aimed at early career researchers, provides travel support for investigators to present on LGMD2A at major scientific conferences. Additionally, C3 has created the first global patient registry for LGMD2A. Our current priorities are to fund research efforts and support collaborations focused on finding a treatment for LGMD2A.

http://dx.doi.org/10.1016/j.nmd.2018.06.132

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Recessive limb-girdle muscular dystrophies in a Brazilian tertiary hospital: epidemiological, clinical and genetic profile

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The limb-girdle muscular dystrophys (LGMD) are a heterogeneous group of autosomal hereditary diseases that share common clinical and laboratory findings such as weakness and atrophy of proximal muscles, often affecting lower extremities first; elevated creatine kinase (CK) levels; and dystrophic findings on muscle biopsy. There is little information regarding the frequency of each LGMD-related mutation in Brazil. Describe the genetic and profile of recessive limb-girdle muscular dystrophies cases from a tertiary hospital from southeastern Brazil. The molecular data analyzes was accomplished by DNA extraction from peripheral blood, followed by analyzes from *ANO5*, *FKRP, SGCD, GAA, CAPN3, SGCA, SGCG, DYSF, SGCB, TCAP* genes through next generation sequencing (NGS panel). From 82 tested patients, 40 (49%) presented any mutation. From this, 29 in homozygosity or compound heterozygosity. Among patients with LGMD2 confirmed diagnosis, there was 11 LGMD2B, 8 with LGMD2A, 5 with LGMD2E, 2 with LGMD2I, 1 with LGMD2G and 2 with LGMD2L, this, not yet described in the Brazilian population. The gender distribution was: 13 male and 16 female. The patients mean age was 37,9 years, and the symptoms onset ranged from 1 to 58 years old, with a mean of 12,3. The mean age at diagnosis was 35.6 years. The mean CK value at diagnosis was 4327 U / L. The lung function test identified 16 patients with normal forced vital capacity, 3 with a mild restrictive pattern and 3 with a severe restrictive pattern. This data was not available in the medical record form 7 patients. The NGS panel was sensitive to detection of mutations related to the LGMD, being more frequent in the genes of dysferlin and calpain 3, similarly to reported in literature. LGMD2I, common in European populations, was less frequent in our cohort.

http://dx.doi.org/10.1016/j.nmd.2018.06.133

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Limb girdle muscular dystrophy: steps toward a comprehensive patient reported outcome

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Disease specific patient reported outcomes measures (PROs) have emerged as clinical devices that are useful to measure disease progression and serve as a validated outcomes for clincal trials. An initial first step is to identify the multitude of symptoms that impact the health and daily function of individuals with limb-girdle muscular dystrophy (LGMD) using a qualitative, patient-directed approach. The LGMDs include over 50 different genetic conditions that result in a shared clinical phenotype. They are characterized by progressive weakness of the shoulder girdle and hip girdle. Some disorders include extra-muscular manifestations, such as joint contractures, but these are dependent on the specific mutations. Studies focusing on the physical, mental and social impact of this disease from the patient's point of view are limited. Interviews with genetically confirmed LGMD patients were conducted using a semi-structured, qualitative, approach. Participants were asked to identify the symptoms and issues that have the greatest impact on their quality of life. Each interview was recorded, transcribed, coded, and analyzed using a qualitative framework technique. Quotes were obtained from patient interviews. Participants provided 1383 direct quotes. 166 potential symptoms of importance to adult LGMD participants were identified. Symptoms were further grouped by like topics into fifteen larger symptomatic themes. Participants most frequently identified: difficulty going upstairs (65); decreased ability to carry a heavy load with arms (44); awareness of disease progression (42); leg weakness (40); arm weakness (35); difficulty rising from a seated position (31); difficulty with personal hygiene (30). There are multiple symptoms and issues that alter the lives of adults with LGMD. These symptoms affect the physical, mental, and social health of patients and may be amenable to medical intervention. Next steps will include development and validation of an LGMD specific PRO through an investigator led LGMD natural history consortium. This tool will be enable rational clinical trial design and a quantitative metric of LGMD disease progression.

http://dx.doi.org/10.1016/j.nmd.2018.06.134

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Limb-girdle muscular dystrophy in Taiwan: a referral center experience

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Limb-girdle muscular dystrophy (LGMD) is a hereditary disease entity characterized by limb-girdle weakness and histologically dystrophic change although genetically heterogeneous. The prevalence of each subtype of LGMD varies among different ethnic populations. This study aims to analyze the phenotypes and genotypes of Taiwanese patients with LGMD in a referral center for neuromuscular diseases. We enrolled 95 patients clinically suspected to have LGMD who have received muscle biopsy and/or genetic analysis in the past 10 years. In this cohort, one patient with type 1B, 5 with 1D, 5 with 2A, 5 with 2B, 6 with 2D, 8 with 2I, 3 with 2G and one with 2N have been diagnosed. The 1B patient with *LMNA* mutation presented with mild limb-girdle weakness and elbow joint contracture but no conduction defect. All 1D patients with *DES* mutation from one family showed predominantly proximal but also distal weakness. Sudden cardiac death occurred in one patient. Muscle pathology of 3 in 5 LGMD2A patients with *CAPN3* mutations showed prominent lobulated fibers. All LGMD2B patients diagnosed by complete dysferlin deficiency showed a bit slower progression, compared with type 2A. Six patients harbored a common homozygous

mutation in *SGCA*, leading to the diagnosis of LGMD2D. All LGMD2I patients with *FKRP* mutations have developed dilated cardiomyopathy and variable degree of respiratory involvement. One suffered from cerebral infarction due to cardiac emboli. Muscle pathology of two in 3 LGMD2G patients with *TCAP* mutations showed vacuolar change. One LGMD2N patient with *POMT2* mutations presented with slowly progressive weakness without significant intelligence impairment. Our study showed that muscle pathology remains helpful in guiding further molecular analyses and is crucial for establishing the genotype-phenotype correlation. We also determined the frequencies for different types of LGMD in our cohort which is important for developing specific care system for each disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.135

P.108

Functional characterization of DNAJB6 J-domain mutations

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Limb-girdle muscular dystrophy type 1D (LGMD1D) is caused by dominant mutations in *DNAJB6*. This ubiquitously expressed co-chaperone interacts with the HSPA (Hsp70) chaperones and promotes their function, and also acts as a powerful suppressor or protein aggregation. Until recently, all of the known LGMD1D-causing mutations in *DNAJB6* were located relatively close to each other within the glycine/phenylalanine-rich (GF) domain of the protein. This domain, whose function remains poorly understood, links the HSPA-interacting J domain and the substrate-binding C-terminal domain. The mutations impair the anti-aggregation activity of DNAJB6 and confer a dominant toxic effect to the cytoplasmic isoform DNAJB6 isoform (DNAJB6b). Some GF-domain mutations have also been shown to interfere with the turnover of DNAJB6; however, not all mutations have been characterized in this respect. The first LGMD1D patients with missense variants in the J domain of DNAJB6 have now been identified. To evaluate their pathogenicity and to gain further insight into the molecular pathomechanisms of LGMD1D, we performed functional studies on two putative disease-causing J-domain variants, p.Ala50Val and p.Glu54Ala. The nearby, presumably harmless variant p.Ser57Leu served as control. In filter trap assay, DNAJB6b constructs with disease-associated variants showed impaired anti-aggregation activity towards polyQ-huntingtin, supporting the causative role of the variants and highlighting the importance of the anti-aggregation defect in the pathogenesis of LGMD1D. Protein turnover studies indicated a reduced turnover rate for p.Ala50Val but not for p.Glu54Ala, suggesting that impaired turnover may not be a universal feature of pathogenic *DNAJB6* variants.

http://dx.doi.org/10.1016/j.nmd.2018.06.136

P.109

Clinical presentation of a new transportinopathy phenotype in a Hungarian family LGMD D2

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We report a LGMD D2 family characterised by an undescribed transportin gene mutation and severe phenotype. In the maternal pedigree an affected child was reported. The mother a 43 year old woman started walking at 15 months, was always weak as a child respect to peers, had proximal weakness primarily affecting lower limbs. A biopsy showed mitochondrial alterations and myofibrillar dissolution. During her second pregnancy at 30 years she underwent a C-section and presented difficulty breathing and felt "paralyzed". She had frequent falls, difficulty swallowing and could not run, keep legs elevated or raise from floor, to climb stairs used handrail. She has reduced vital capacity on spirometry (FVC 57%). On last examination she had pigeon toe-feet, kyphoscoliosis, weakness of triceps and deltoid (2/5 MRC scale), biceps, pectoralis, wrist extensors (4/5). Her 12 year old son presented signs of weakness since first year. He started walking at one year, can raise from chair or laying position using hands. The biopsy showed type 1 fiber predominance (92%) both fiber type atrophy, myofibrillar disorganization. He walked 3 km up to 10 years, but walks only 300 metres now, feels fatigued and falls. He has a waddling gait, Gowers sign, climbs stairs using handrail. He has difficulty swallowing. On examination he could not raise from laying position, without grasping his knees. His grip is weak. DTR were absent. Muscle MRI was performed in both mother and son and showed marked generalized muscle atrophy. An heterozygous frameshift deletion c2767delC(pArg923Aspfs17) in exon 23 of *TNPO3* gene was identified by Whole Exome Sequencing, confirmed by Sanger sequencing both in mother and son, absent in another unaffected son, segregating with disease within the family. This variant identified in this Hungarian family appears associated to an intermediate phenotype LGMD/congenital myopathy leading to early, progressive weakness although with different disease severity in mother and son.

http://dx.doi.org/10.1016/j.nmd.2018.06.137

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Limb girdle muscular dystrophy type 1G caused by D378N mutation in *HNRPDL* gene with distal muscle weakness in a Chinese family

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Autosomal dominant limb-girdle muscular dystrophies (LGMD type 1) are a group of clinically and genetically heterogeneous diseases characterized by weakness and wasting of the pelvic and shoulder girdle muscles. Eight subtypes of LGMD1 (LGMD1A-1H) have been described. Causative mutations are known for seven of them, except for LGMD1H. To date, only two LGMD1G families have been reported, including a Caucasian-Brazilian family and a Uruguayan family. D378N and D378H mutations in *HNRPDL* gene were found in these two families respectively. To investigate a Chinese family with dominantly inherited myopathy, following clinical evaluation and the identification of the dystrophic histological phenotype with rimmed vacuoles on muscle histology, exome sequencing was performed. Exome sequencing of the proband in this family identified a heterozygous c.1132G>A (p.D378N) mutation in *HNRPDL* gene, which co-segregated with disease phenotype in the family. Interestingly, the patients reported here did not show/develop progressive flexion limitation of toes and fingers, which was recognized as a classic presentation in LGMD1G. Moreover, three patients had distal limb weakness as well as proximal weakness, which were not found in the Brazilian family or the Uruguayan family. The site of mutation in HNRPDL identified in all three families is at p.D378, indicating that p.D378 might represent a mutational hotspot. To our knowledge, this is the third family with LGMD1G worldwide. Our findings widen the spectrum of phenotypes in LGMD caused by *HNRPDL* mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.138

DMD CLINICAL THERAPIES I

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Preservation of function over time as measured by North Star ambulatory assessment in boys with nonsense mutation Duchenne muscular dystrophy treated with ataluren

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Ataluren is the first drug approved to treat the underlying cause of disease in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD), by promoting readthrough of a nonsense mutation to produce full-length func-

tional dystrophin protein. ACT DMD was a 48-week, multicenter, randomized, double-blind, placebo controlled study that compared the efficacy and safety of ataluren vs placebo in ambulatory boys with nmDMD. ACT DMD enrolled boys aged 7—16 years with nmDMD and a baseline 6-minute walk distance (6MWD) of 150 m or more, and having ≤80% of the predicted normal value at baseline (n=228). The North Star ambulatory assessment (NSAA) is a validated tool that assesses disease progression in ambulatory boys with DMD. NSAA is comprised of 17 tasks that patients are evaluated on at each clinic visit, with the possible values for each item being 0, 1, or 2, where 0=unable to perform task, 1=performs with difficulty and 2=able to perform. In the present analysis, loss of function (failures) from 17 tasks was evaluated for each patient (i.e., 2 to 0, or 1 to 0) at various time points over the entire study duration. The average cumulative number of failures over time was then obtained over all study patients for each treatment group, which can be plotted to show the temporal profile of treatment. Graphically, the curve for the placebo is uniformly higher than that of ataluren. The ratio of the above two curves can then be used as an overall measure of treatment effect (i.e., treatment divided by placebo) using the method by Lin Wei Yang Ying. This analysis resulted in a ratio of 0.73 (95% CI, 0.55-0.97; p=0.027), indicating that, ataluren treatment significantly reduces the cumulative number of failures by 27% over 48 weeks compared to placebo. Separation between these two curves is seen as early as 32 weeks and continues to diverge over the 48 weeks. The results suggest preservation of physical function with ataluren therapy in ambulatory boys with nmDMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.139

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STRIDE™: A patient registry study examining the use of ataluren (Translarna™) in patients with nonsense mutation muscular dystrophy (nmDMD)

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The STRIDE™ Registry is an ongoing, multicenter, observational study aimed at building a patient data repository to provide real world experience regarding the treatment patterns for ataluren in routine clinical practice. Ataluren (Translarna™) is the first-approved treatment for nonsense mutation Duchenne muscular dystrophy (nmDMD) in the European Union in ambulatory patients aged 5 years and older. The study is being conducted in the countries in which the drug is commercially available. An enrollment of approximately 200 patients was targeted, based in part on the size of the nmDMD population in the EU. Patients are being followed for at least 5 years from the date of a patient's enrollment, or until withdrawal of patient consent, or death, whichever occurs first. Baseline data (as of 31.01.2018) from a cohort of 154 patients (98.1% males, n=151) with nmDMD from sites across 12 counties were analyzed in terms of demography and clinical manifestations of nmDMD. In this cohort, the median age was 10.2 (5.0, 45.4) years; nmDMD was most frequently diagnosed between the ages of 5-10 years (n=74, 48.1%), and the median age at genetic confirmation was 5.5 years (0.02, 39.1). The median age of symptomatic detection was 2.5 years (0, 30) with a mean time (SD) between first clinical/biochemical symptoms and nmDMD diagnosis confirmation (i.e., identification of dystrophin gene mutation) is 3.0 years (2.5). The exclusion of female carriers from the analysis had minimal impact on median age (10.1 years; min, max: 5, 22.8) and median age at genetic confirmation (5.4 years; min, max: 0.9, 15.6). Additional descriptive statistics from demographic data are forthcoming. These data suggest a need for increased awareness of nmDMD symptoms in order to reduce delays in diagnosis; the later median age at diagnosis observed here relative to recent results from the global DMD population (3.4 - 4.3 yrs) suggests that some countries may still face challenges with genetic testing for nmDMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.140

P.113

Long-term effect of ataluren in fourteen patients with nonsense mutation Duchenne muscular dystrophy

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Nonsense mutation Duchenne muscular dystrophy (nmDMD) is a rare, X-linked genetic disorder that results in a decline in function, loss of ambulation and early death due to respiratory or cardiac failure. Ataluren is conditionally approved by the European Medicines Agency for the treatment of ambulatory patients aged ≥ 5 years with nmDMD. It is essential to know the long-term effect of this treatment. To know the long-term effect (over a 4-year Interval) of ataluren treatment in 14 patients at the end of the ACTm extensions of the clinical trial performed in our center. From the fourteen patients, seven started in the placebo group and seven in the treatment group. Placebo arm (First 48 week of clinical trial - delayed start ataluren): 9-12 years old, 6MWT: 282 - 444 meters, all the patients missed the walk (36 months average after the start of the trial). Arm treatment (early start ataluren): 9 - 12 years old, 6MWT: 250 - 431 meters. Three patients lost the walk: 2 who started the clinical trial with 6MWT less than 300 meters and one over 10 years of age at the beginning of the clinical trial. Of the four patients who maintained the walk, three remain stable on the walk with a loss less than 75 meters in the 6MWT in 4 years and one patient has lost 160 meters. In relation to North Star Ambulatory Assessment, the loss of motor capacities is lower in the treated group than in the delayed start ataluren treatment patients. We observed a benefit of treatment with ataluren in the subgroup of patients under 10 years of age and who have a walk greater than 350 meters at the beginning of treatment. The long-term follow-up with functional motor scales will allow to identify good responders to these treatments.

http://dx.doi.org/10.1016/j.nmd.2018.06.141

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Vamorolone as a replacement for corticosteroids in Duchenne muscular dystrophy: phase 2a results in 48 DMD boys

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Vamorolone (VBP15) is a first-in-class dissociative steroidal drug that binds the glucocorticoid and mineralocorticoid receptors with similar affinity as prednisone but has lost most gene transcriptional activity due to loss of ligand/receptor dimerization and binding to gene promoters. This dissociative property elicits retention of anti-inflammatory activities in animal models of chronic inflammatory states, yet loss of several corticosteroid safety concerns. Phase 1 data in healthy adult subjects confirmed loss of bone morbidities and insulin resistance using serum biomarkers reflective of these clinical safety

concerns. Here, we report first-in-patient studies in 48 DMD boys, age 4 to <7 years carried out by the Cooperative International Neuromuscular Research Group (CINRG), ReveraGen BioPharma, and TRiNDS. Enrollment criteria included steroid-naïve, antibodies to varicella, and ability to stand from the floor. The initial trial was VBP15-002, an open label multiple ascending dose study (0.25, 0.75, 2.0, 6.0 mg/kg/day dose groups; 12 per group), with two weeks treatment, and two weeks washout. Outcomes were safety, tolerability, pharmacokinetics, pharmacodynamic biomarkers bridged to potential safety concerns, metabolites in safety testing (MIST), exploratory biomarkers of efficacy, and exploratory pharmacodynamic biomarkers for efficacy and safety. Subjects then had the option to enroll into the VBP15-003 24-week extension study, continuing with the same dose. Outcomes were clinical efficacy (time to stand, six-minute walk, 10-meter run/walk, and others), and clinical safety (change in body mass index). Upon completion of the VBP15-003 study, subjects were given the option to enroll in a 2-year long-term extension study (VBP15-LTE). The LTE included dose escalation options. Results of the VBP15-002 and VBP15-003 trials are presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.142

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Targeting NADPH oxidases in models of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a severe X-linked muscular disease that causes premature death and for which no cure exists. We have shown previously that *in vitro* treatment of dystrophic myotubes and excised muscles with diapocynin, a dimer of the classically used NADPH oxidase (NOX) inhibitor apocynin, ameliorated several molecular events involved in DMD pathogenesis, of which ROS production, phospholipase A2 activity, Ca2+ influx and sarcolemmal integrity. Here, we report on the *in vivo* effects of diapocynin and apocynin in mdx5Cv dystrophic mice, a model of DMD. Diapocynin but not apocynin enhanced spontaneous locomotor activity, rescued voluntary wheel running capabilities, and ameliorated diaphragm structure of dystrophic mice. Diapocynin and apocynin were equally potent at increasing the resistance to fatigue of triceps surae muscles exposed to repeated isometric contractions in situ and at preserving sarcolemmal integrity as evidenced by Evans blue dye uptake. Furthermore, microarray analyses showed a tendency of the treatments to correct gene expression in dystrophic mice. To further validate NOXes as novel therapeutic target in DMD, novel tools for monitoring NOX activity in muscle fibres have been evaluated and new NOX2 and NOX4 inhibitors have been tested in dystrophic cultures and isolated muscles. The results of this study show the potential of targeting NOXes in DMD animal models.

http://dx.doi.org/10.1016/j.nmd.2018.06.143

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Edasalonexent, an NF-κB Inhibitor, slows disease progression over more than a year compared to control period in 4 to 7 year old patients with Duchenne muscular dystrophy

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Edasalonexent (edasa, CAT-1004), an oral small molecule inhibiting NF-κB, is being investigated as a potential foundational therapy for patients with any *DMD* mutation. In a phase 2 randomized, placebo-controlled trial with an open-label-extension enrolling 31 steroid-naïve 4-7 year old boys with DMD, edasa was studied at doses of 67 and 100 mg/kg. A prior off-treatment control period in most boys enabled off- and on-treatment comparisons. Data were analyzed after up to 60 weeks of edasa treatment, and ongoing analysis of additional data will be presented. To inform future development, a 133 mg/kg dose was also assessed for safety and tolerability. Disease progression in the off-treatment control period corresponded with off-steroid natural history of boys in this age range. With edasa 100 mg/kg for up to 60 weeks, there was clinically meaningful slowing of disease progression compared to off-treatment control period as assessed by timed function tests (TFTs; 10-meter walk/run, time-to-stand and 4-stair climb) and the North Star Ambulatory Assessment (NSAA). Muscle enzymes decreased beyond >12 weeks ($p<0.05$), as did CRP ($p<0.05$). Lower leg muscle MRI-T2 and fat fraction also were consistent with slowing of disease progression in contrast to off-treatment progression. Edasa was well tolerated at all doses without safety signals. The most common adverse events were gastrointestinal, typically mild and transient. Height and weight increased age-appropriately, and heart rate declined toward age-normative values. Treatment with edasa substantially delayed disease progression compared to an off-treatment control period as assessed by changes in TFTs and NSAA. Changes in muscle enzymes, MRI, and heart rate provided additional support of positive effects. Edasa has potential to be disease-modifying in DMD patients and does not appear to have the adverse effects associated with high-dose steroids. A Phase 3 study is planned based on these positive efficacy and safety data.

http://dx.doi.org/10.1016/j.nmd.2018.06.144

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Edasalonexent, an oral NF-κB inhibitor, in development for treatment of Duchenne muscular dystrophy: the phase 3 POLARIS study design

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In patients with DMD, muscle NF-κB is activated from infancy, driving inflammation, muscle degeneration and inhibiting muscle regeneration. Glucocorticoids inhibit NF-κB and block inflammation; they clinically delay disease progression, but significant side effects limit their use. Edasalonexent (CAT-1004), a small molecule inhibiting NF-κB, has shown positive preclinical effects on skeletal muscle, diaphragm and heart in DMD, and is being investigated as a potential oral foundational therapy for any DMD mutation. A phase 2 study with open-label extension (OLE) in 4 to 7 year old boys with DMD showed clinically meaningful slowing of disease progression compared to a prior off-treatment control period as assessed by timed motor function test (TFT) speeds and the North Star Ambulatory Assessment (NSAA). Positive effects were also seen on muscle MRI measures, muscle enzymes and C-reactive protein as a biomarker of inflammation. Height and weight increased age-appropriately, and heart rate declined toward age-normative values. Phase 1 and phase 2 studies have shown no safety signals and have demonstrated inhibition of NF-κB. The phase 3 POLARIS study is designed to enroll boys from their 4th to 7th birthdays with genetically confirmed DMD with any mutation who are able to complete the 4-stair climb and time-to-stand in <10 sec. Key exclusion criteria will include the use of glucocorticoids in the last 6 months, or recent use of investigational therapies. Edasalonexent will be given in three divided doses with meals for 52 weeks to be followed by an OLE. The NSAA will be the primary endpoint with TFTs as secondary endpoints. Approximately 125 boys will be enrolled in a 2:1 ratio, active:placebo. Additional assessments planned are periodic ambulatory heart rate monitoring and DXA for body composition and bone density. Edasalonexent is being developed as a disease-modifying foundational therapy in DMD patients regardless of mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.145

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Assessing the safety and efficacy of MNK-1411 in patients with Duchenne muscular dystrophy in a multicenter, double-blind, placebo-controlled, multiple-dose study

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Duchenne muscular dystrophy (DMD) is a recessive X-linked neurodegenerative disorder with disease symptoms typically manifesting in males by age 6, resulting in weakness and loss of ambulation from progressive muscle degeneration. MNK 1411 is a 24—amino-acid synthetic adrenocorticotropic hormone analogue and melanocortin receptor (MCR) agonist. MNK-1411 is hypothesized to slow DMD disease progression via potential steroid-dependent and steroid-independent anti-inflammatory properties and by directly attenuating muscle damage that may occur via activation of MCRs on relevant tissues and cells (eg, macrophages, lymphocytes, skeletal muscle). Outlined here is the design for a phase 2, multicenter, double-blind, placebo-controlled, multiple-dose study evaluating the safety and efficacy of MNK-1411 in male patients aged 4 to 8 years with DMD (ClinicalTrials.gov Identifier: NCT03400852). Patients will be randomized 2:2:1:1 into the 24-week double-blind phase and receive weight-based doses of subcutaneous MNK-1411 or volume-matched placebo (2x/wk). The 4 treatment groups comprise Group A, 0.5-mg MNK-1411 (0.5 mL) for patients >20 kg or 0.4-mg MNK-1411 (0.4 mL) for patients ≤20 kg; Group B, 0.25-mg MNK-1411 (0.25 mL) for patients >20 kg or 0.2-mg MNK-1411 (0.2 mL) for patients ≤20 kg; Group C, 0.5-mL or 0.4-mL placebo; and Group D, 0.25-mL or 0.2-mL placebo. Patients who complete the blinded phase will be eligible to enter a 24-week open-label extension phase and continue receiving the same volume of MNK-1411. The primary efficacy endpoint is change from baseline in the 10-meter walk/run at Week 24. Adverse events will be monitored throughout the study. Approximately 130 patients will be enrolled at 50 global sites in this trial, which will have 80% power to detect a treatment difference between groups at a significance level of 0.05. This ongoing study will potentially provide data to support the safety and efficacy of MNK-1411 for treatment of patients with DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.146

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Tamoxifen in Duchenne muscular dystrophy: rationale and protocol for a multicentre, randomised, double-blind, placebo-controlled, phase 3 safety and efficacy 48-week trial

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Most current research on therapeutics of Duchenne muscular dystrophy (DMD) focuses on correcting the gene defect. However, as there are more than 250 mutations in the human dystrophin gene, this approach will treat only a small percentage of patients and will be expensive. Using the mouse DMD model it could be shown that tamoxifen (TAM), given orally for periods of 2 or 15 months, results in almost full recovery of force and structure of muscles. TAM is one of the most efficacious drugs ever investigated in an animal model of DMD. Our aim is to investigate whether TAM treatment, compared to placebo, reduces the disease progression in DMD patients. We are setting up an international (France, Germany, Greece, Spain, Switzerland, United Kingdom, The Netherlands, Turkey) randomised double blind placebo controlled 48-week clinical trial with a core population (group A) of 79 ambulant 6.5 to 12 years old DMD patients that are on a stable standard treatment with glucocorticoids. Parallel we will include 16-20 non-ambulant patients age 10 to 16 years who do not receive glucocorticoids (group B) to obtain efficacy and safety data in a broader DMD population. All patients will receive 20 mg of TAM or placebo once daily over 48 weeks. The primary outcome for group A is the motor function measure (MFM) D1. In group B the MFM D2 is the primary endpoint, allowing extrapolation of MFM D2 data from the group A population. In addition, to investigate whether longterm TAM treatment can slow muscle degeneration, quantitative thigh muscle magnetic resonance imaging will be performed. The study aims to describe an efficacy and safety profile for tamoxifen in the treatment of DMD patients. The purpose of this study is to evaluate if TAM shows positive effects on muscle function and muscle force in comparison to placebo in DMD-patients. Recruitment is expected to start in June 2018.

http://dx.doi.org/10.1016/j.nmd.2018.06.147

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Epicatechin improves biomarkers of muscle growth and regeneration, oxidative stress, and NO reserve, and improves skeletal muscle exercise response in non-ambulatory DMD patients with presymptomatic cardiomyopathy

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(+)-epicatechin is a structural homologue of a family of PGC1-alpha activating steroid hormones that promote mitochondrial biogenesis and induce skeletal muscle regeneration. Epicatechin stimulates mitochondrial biogenesis and improves muscle structure and function in *Mdx* mice and human Becker muscular dystrophy. We conducted an open-label escalating dose study of epicatechin in non-ambulatory DMD patients with preclinical cardiomyopathy in support of a Phase II study. 10 participants received (+)-epicatechin 25mg PO BID or 25mg PO TID for 8 weeks. A 5-patient cohort is presently undergoing treatment at and 75mg PO TID. Pre- and post-assessments included evaluation of plasma follistatin, myostatin, nitrate/nitrite ratio, troponin I, and protein carbonylation, and assisted 6-minute cycle test. Assessments also included tagged cardiac strain imaging by cMRI and speckle-tracking echocardiography, and safety laboratory panels. Across the first 2 dose levels, follistatin levels increased to 200% of baseline ($p<0.0001$) and follistatin:myostatin increased to 194% of baseline ($p<0.0001$). Nitrite/nitrates increased to 150% of baseline ($p<0.0001$). Troponin I decreased to 70% of baseline ($p<0.0001$). Protein carbonylation decreased to 69% of baseline ($p<0.0001$). Assisted 6-minute cycle test performance increased to 112% of baseline ($p<0.0001$). The highest evaluated dose (75mg/day) was well tolerated. Evaluation of data from all 3 dose cohorts and for cardiac imaging data is underway. (+)-epicatechin improves circulating biomarkers of muscle growth and regeneration, increases circulating stores of NO, and decreases oxidative stress. It is the only oral compound ever demonstrated to increase plasma follistatin and improve follistatin:myostatin ratio, which may comprise a future pharmacodynamic biomarker. The small but significant increase in exercise performance is consistent with a short-duration exercise training effect.

http://dx.doi.org/10.1016/j.nmd.2018.06.148

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Phase II study of TAS-205 in patients with Duchenne muscular dystrophy: subgroup analyses

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Inflammation has been included in the pathological process of Duchenne muscular dystrophy (DMD). Prostaglandin D2 (PGD2) is produced by various

inflammatory cells, and hematopoietic PGD synthase (HPGDS) is shown to be expressed in the necrotic muscles of DMD patients. The primary objective of this study was to evaluate the efficacy of TAS-205, a specific inhibitor of HPGD2S, orally administered twice daily for 24 weeks, compared with placebo in ambulatory DMD patients. For this double-blind study, subjects were evenly randomized to one of the three groups, a low-dose (6.67 to 13.33 mg/kg/dose), high-dose (13.33 to 26.67 mg/kg/dose), or placebo group. A total of 36 subjects were enrolled. The primary endpoint was the change from baseline in the measured 6-minute walk distance (6MWD) at week 24. The mean value difference from the placebo group was 13.5 m for the low-dose group and 9.5 m for the high-dose group. Subgroup analyses of the primary endpoint and secondary endpoints (motor function, muscle volume) were performed with two baseline 6MWD categories, <350 m and ≥350 m. The differences of almost all functional parameters of motor evaluations between the TAS-205 high-dose group and the placebo group tended to be larger in the group with baseline 6MWD ≥350 m than in that with baseline 6MWD <350 m. The muscle volume index (%MVI), evaluated using CT, of the thigh and lower leg significantly decreased at week 24 in the placebo group, which confirmed the reliability of the method. The %MVI reduction of the thigh and lower leg tended to be lower in the TAS-205 group than that in the placebo group. Results of model and correlation analyses in the patients with baseline 6MWD ≥350 m using the alterations of baseline 6MWD and lower leg %MVI at week 24 indicated their relatively high relationship. It was suggested that these data confirm the clinical benefit of TAS-205 in terms of preserving muscle function.

http://dx.doi.org/10.1016/j.nmd.2018.06.149

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A phase III clinical study assessing the efficacy and safety of idebenone in patients with Duchenne muscular dystrophy taking concomitant glucocorticoids (SIDEROS)

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Duchenne muscular dystrophy (DMD) is a disease resulting in progressive loss of respiratory function. Idebenone, a short-chain benzoquinone, acts on the mitochondria to increase energy production and decrease oxidative stress. In the randomized, placebo-controlled Phase III DELOS study, the effects of idebenone on respiratory function were investigated in 10-18-year-old DMD patients not taking concomitant glucocorticoids (GCs). Idebenone slowed the rate of respiratory function decline as demonstrated by a statistically significant difference versus placebo in peak expiratory flow (expressed as percent predicted; PEF%p) in addition to other respiratory outcome measures. SIDEROS is a Phase III, randomized, placebo-controlled study investigating the safety and efficacy of idebenone in 266 DMD patients taking GCs in approximately 64 centers in the US, EU and Israel. Inclusion criteria dictate that participants are 10 years or older, are in the linear respiratory decline phase (forced vital capacity [FVC%p] between 80 and 35%p) and are taking GCs for at least 12 months prior to baseline and throughout the study time-course. Patients will be randomized (1:1) to receive either idebenone (900 mg/day) or placebo, taken three times daily with meals. The treatment duration is 78 weeks. Patients who complete SIDEROS will also be eligible to participate in an open-label extension study, in which all patients will receive idebenone. The primary endpoint of SIDEROS is the change from baseline in FVC%p assessed by clinic-based spirometry measurements. Other efficacy assessments include PEF, forced expiratory volume in 1 second, peak cough flow, inspiratory flow rate, blood oxygen saturation levels, end-tidal CO2 readings, occurrence of bronchopulmonary adverse events, use of systemic antibiotics and hospitalizations due to respiratory causes.

http://dx.doi.org/10.1016/j.nmd.2018.06.150

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A randomized, placebo-controlled, double-blind, phase 1b/2 study of the novel anti-myostatin adnectin RG6206 (BMS-986089) in ambulatory boys with Duchenne muscular dystrophy

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Inhibition of myostatin, a negative regulator of muscle growth, has been shown to increase skeletal muscle mass in several species. RG6206 (BMS-986089) is a potent, novel anti-myostatin adnectin shown to inhibit myostatin activity in healthy adults. This phase 1b/2 study (NCT02515669) assessed the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics of RG6206 in ambulatory boys with Duchenne muscular dystrophy (DMD). Forty-three ambulatory boys with DMD, aged 5-10, were randomized to receive weekly subcutaneous RG6206 (4-50 mg) or placebo. The primary endpoint was safety and tolerability over 24 weeks. Secondary endpoints were PK of RG6206, frequency of anti-drug antibodies (ADAs), effect on serum myostatin levels and MRI imaging. Exploratory outcomes included 4-stair climb velocity (4SC), 6-minute walk test distance (6MWT) and DXA imaging. No clinically significant changes in laboratory values, vital signs or ECG parameters were observed. Adverse events (AEs) were mostly mild; the most common drug-related AE was mild-to-moderate cutaneous injection site reactions (n=7, 21.9%). ADAs were observed in one patient, who had a positive titer at baseline with no post-treatment boost. RG6206 serum concentrations increased with dose and were accompanied by dose-dependent reduction in free myostatin at all dose levels. RG6206 was well tolerated. DXA imaging data showed increased lean body mass with RG6206 treatment vs. placebo. MRI imaging of the right thigh suggested that RG6206 had positive effects on muscle composition, with an increase in contractile, and lesser increase in non-contractile, tissue compared with placebo. However, this response did not appear to be dose dependent. Post hoc analyses of the correlation between MRI/DXA imaging data and functional measures including 4SC and 6MWT will be presented. An ongoing 48-week open-label phase of this study and a Phase 2/3 study will further evaluate RG6206 in ambulatory boys with DMD (NCT03039686).

http://dx.doi.org/10.1016/j.nmd.2018.06.151

DMD CLINICAL THERAPIES II

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Eteplirsen is well tolerated in adults with mild or moderate renal impairment

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Duchenne muscular dystrophy (DMD) is a rare, X-linked, fatal, neuromuscular disease caused by *DMD* gene mutations that disrupt the dystrophin messenger ribonucleic acid (mRNA) reading frame and prevent production of functional dystrophin protein. Eteplirsen is a phosphorodiamidate morpholino oligomer (PMO) approved by US-FDA for treatment of DMD patients with mutations amenable to exon 51 skipping, Eteplirsen excludes exon 51 to restore the dystrophin mRNA reading frame and enable translation of internally shortened dystrophin protein. PMOs have uncharged backbones and bind in a sequence-specific manner to RNA targets through Watson-Crick base pairing. PMOs represent a unique chemistry, structurally and biologically distinct from other synthetic antisense ribonucleic acid therapeutics, such as phosphorothioates (PSOs). Toxicities observed with PSOs have not been observed in nonclinical or clinical studies of eteplirsen. In DMD patients studied, approximately 64% of the total systemic clearance of eteplirsen 30 mg/kg (approved dose) is via renal excretion. The pharmacokinetics (PK), safety and tolerability of eteplirsen in male volunteers with mild (estimated

glomerular filtration rate [eGFR] ≥60 to <90 mL/min; n=8) or moderate (eGFR ≥30 to <60 mL/min; n=8) renal impairment was evaluated in a single-dose, parallel-group study with 30 mg/kg IV eteplirsen and compared to demographically-matched men with normal renal function (n=9). All enrolled patients completed the study. Total plasma clearance decreased by 27.5% (mild group) and 60.6% (moderate group), with proportional reductions in renal clearance (22.7% and 56.6%, respectively) and higher overall exposure compared to the normal group. The single IV dose appeared to be well tolerated by all groups. PMO eteplirsen was well tolerated across renally impaired and normal groups. Exposure to eteplirsen increased as a function of decrease in renal clearance.

http://dx.doi.org/10.1016/j.nmd.2018.06.152

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Eteplirsen treatment attenuates respiratory decline in ambulatory and non-ambulatory patients with Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) patients experience progressive degeneration of skeletal muscles including those involved in respiration. Well characterized respiratory decline in glucocorticoid-treated DMD patients includes forced vital capacity % predicted (FVC%p) decline ≥5% per year between the ages of 10 and 18 years. We evaluated eteplirsen treatment effect on FVC%p annual change in three eteplirsen clinical trials compared to well-matched natural history controls from the Cooperative International Neuromuscular Research Group (CINRG). Age-based mixed model analyses were conducted to determine FVC%p annual change (slope) for eteplirsen-treated patients and CINRG controls. Patients in the CINRG control (n=20) were amenable to exon 51 skipping, on glucocorticoids, and had FVC%p assessments between the ages of 10 and 18 years. Patients in the eteplirsen clinical trials (n=74) were amenable to exon 51 skipping, on glucocorticoids, and only FVC%p assessments between the ages of 10 to 18 years were included in the analysis. Study 201/202 was conducted over 216 weeks and enrolled ambulatory patients. Study 204 was conducted over 96 weeks and enrolled primarily non-ambulatory patients. Study 301 is an ongoing study which enrolled ambulatory patients; an interim week 96 analysis is presented. In Study 201/202 the annual change in FVC%p in (n=12) eteplirsen-treated patients was -2.19% compared to -6.00% in CINRG controls ($p<0.001$). In study 204 annual change in FVC%p in (n=20) eteplirsen-treated patients was -3.66% compared to -6.00% in CINRG controls ($p=0.004$). In an interim analysis of Study 301 annual change in FVC%p in (n=46) eteplirsen-treated patients was -3.79% compared to -6.00% in CINRG controls ($p=0.017$). Significant and clinically meaningful attenuation of FVC%p decline was seen in eteplirsen-treated patients compared to CINRG controls across three clinical trials in both ambulatory and non-ambulatory DMD patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.153

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Respiratory function decline in eteplirsen-treated patients diverges from natural history comparators over time

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Duchenne muscular dystrophy (DMD) patients experience progressive degeneration of skeletal muscles including those involved in respiration, and respiratory decline is linked to mortality. Onset of respiratory decline precedes increasing levels of clinical management as FVC%p falls below established thresholds. The goal of treatment is to delay time to these thresholds. While motor function in eteplirsen-treated patients in study 201/202 diverges from natural history after 1 year of treatment, it is unclear if respiratory function follows a similar pattern. We evaluated eteplirsen treatment effect in study 201/202 on FVC%p over time compared to well-matched natural history controls from the Cooperative International Neuromuscular Research Group (CINRG) to determine if respiratory decline exhibits a pattern similar to what has been described for motor function. In study 201/202 pulmonary function tests were performed in all patients (n=12) every 24 weeks over the course of 216 weeks of eteplirsen therapy. FVC%p was plotted over time for study 201/202. This was compared to FVC%p of baseline age and FVC%p-matched CINRG patients over the course of 4 years to determine if eteplirsen-treated patients diverged from the CINRG patients. 2 cohorts of CINRG patients were used as comparators: The All CINRG cohort (n=75), and genotyped CINRG cohort (n=67). Eteplirsen-treated patients in study 201/202 had a similar baseline and similar decline to the All CINRG and genotyped CINRG cohorts for the first year, and a divergence appeared after year 2 which continued to widen over the 4-year period. At year 4 a difference of approximately 10% FVC%p favored eteplirsen treatment in comparison to both CINRG cohorts. The temporal pattern of divergence of respiratory function in eteplirsen-treated patients from natural history is similar to the pattern of divergence seen for motor function.

http://dx.doi.org/10.1016/j.nmd.2018.06.154

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Identification of potent, muscle-targeting investigational stereo-pure oligonucleotides for exon 53 DMD therapy

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Wave life sciences is developing investigational stereopure exon-skipping oligonucleotides as potential disease-modifying therapies for the treatment of patients with Duchenne muscular dystrophy (DMD). Wave's proprietary technologies enable the production of stereopure oligonucleotides in which stereochemistry at each phosphorothioate position is precisely controlled. WVE-210201, which targets exon 51 in the dystrophin (DMD) gene, is currently being studied in a Phase 1 clinical trial in DMD patients amenable to exon 51 skipping. Wave has also designed stereopure oligonucleotides to target exon 53 in the DMD gene. *In vitro* experiments were conducted in DMD patient-derived myoblasts with Δ45-52 mutation. Cells were treated with oligonucleotides under gymnotic (free uptake) conditions and then analyzed for exon skipping efficiency by Taqman assay and protein quantification by western blot. Stereopure oligonucleotides showed dose-dependent exon 53 skipping efficiency and protein restoration when normalized to wild-type myoblasts. These results were consistent across cell culture conditions and were further confirmed in a second DMD patient myoblast cell line (Δ52). Stereopure oligonucleotides led to negligible activation of the TLR9 innate immune receptor in a reporter assay, and negligible activation of cytokines when incubated with healthy human peripheral blood mononuclear cells (PBMCs) ex vivo and *in vivo* in mice. A single 30 mg/kg intravenous dose of oligonucleotide to a dystrophin deficient mouse model (mdx-23) rapidly penetrated muscles (quadriceps, gastrocnemius, heart and diaphragm) 24 hours after administration, as detected by both viewRNA IHC assay and hybridization ELISA. These studies support further development of a stereopure oligonucleotide as a potential treatment for patients with DMD amenable to exon 53 skipping.

http://dx.doi.org/10.1016/j.nmd.2018.06.155

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A phase II, dose finding study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of NS-065/NCNP-01 in boys with Duchenne muscular dystrophy

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The objective of the study was to evaluate the safety, tolerability, pharmacokinetics and effect on induction of dystrophin protein of high (80mg/kg) and low (40mg/kg) dose NS-065/NCNP-01 for the treatment of Duchenne muscular dystrophy (DMD) caused by dystrophin gene deletion mutations amenable to exon 53 skipping. Additional objectives include muscle function and strength and pharmacodynamics. Dystrophin deletion mutations cause out-of-frame translation of the dystrophin mRNA and absence of muscle dystrophin. Functional gene product can be restored by exon skipping with a goal to ameliorate disease progression. NS-065/NCNP-01, a novel antisense oligonucleotide, has exon 53 skipping activity designed to be effective in DMD patients who have dystrophin deletions comprising exons 43-52, 45-52, 47-52, 48-52, 49-52, 50-52, or 52 alone. The phase II study in North America, NS-065/NCNP-01-201 (ClinicalTrials.gov identifier: NCT02740972), is a dose finding, multiple center study of NS-065/NCNP-01 in glucocorticoid-treated boys, 4-9 years of age, with DMD. Two cohorts, each comprising 8 participants, were treated with weekly intravenous infusions of NS-065/NCNP-01 for 24 weeks. The first four weeks of treatment for each cohort was double-blind and placebo-controlled, followed by open label treatment with NS-065/NCNP-01 for 20 additional weeks. There were no serious or severe adverse events related to the drug treatment in either cohort. The primary efficacy outcome measure was Western blot assessment of muscle dystrophin expression, determined by sampling muscle tissue prior to drug treatment and following week 24 of treatment. Additional assessments include dystrophin expression by immunofluorescence, mass spectrometry and RT-PCR, timed function and strength measures and pharmacokinetic sampling. All participants completed NS-065/NCNP-01-201 and have enrolled in a long-term treatment follow up study, NS-065/NCNP-01-202. Results of the study will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.156

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A Japanese phase I/II study of NS-065/NCNP-01, exon 53 skipping drug, in patients with Duchenne muscular dystrophy - a dose-finding study

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Duchenne muscular dystrophy (DMD) is an X-linked inherited progressive disease, caused by a mutation in the dystrophin gene. Exon skipping therapy uses a synthesized antisense oligonucleotide designed to skip the specific exon to change out-of-frame to in-frame in the dystrophin mRNA, thereby inducing the expression of functional dystrophin protein. NS-065/NCNP-01 is a novel morpholino oligomer discovered by NCNP and Nippon Shinyaku Co., Ltd. NS-065/NCNP-01 targets exon 53, to serve as effective treatment for DMD patients with deletion of exons 43-52, 45-52, 48-52, 49-52, 50-52 or 52 of dystrophin gene. In 2013, NCNP conducted the first-in-human study as an investigator-initiated clinical study. 10 DMD subjects were assigned to 3 dose group (1.25, 5 and 20 mg/kg), and received weekly treatment for 12 weeks. The results demonstrated NS-065/NCNP-01 was well tolerated and one patient received 20 mg/kg showed high efficiency of exon 53 skipping and expression of dystrophin protein. Given the result of the investigator-initiated clinical study, we planned phase I/II dose-finding, multicenter study (study No: NS065/NCNP-01-P1/2, JapicCTI-163291) to confirm efficacy, safety and pharmacokinetics of higher doses of NS-065/NCNP-01. 16 Japanese DMD patients, age of 5-12 years, amenable to exon 53 skipping were assigned to 40 or 80mg/kg dose group and treated with weekly infusions of NS-065/NCNP-01 for 24 weeks. Dose-dependent increase in Cmax and AUC were observed and there were no significant adverse events and adverse drug reactions in either doses. Furthermore, primary efficacy assessment evaluated dystrophin expression by western-blot and immunofluorescence, and exon 53 skipping levels by RT-PCR, using muscle biopsy specimens obtained at pre and post-treatment (12 or 24weeks). Motor function tests were also performed as secondary efficacy assessment. We report efficacy, safety and pharmacokinetics of NS-065/NCNP-01 obtained by phase I/II study.

http://dx.doi.org/10.1016/j.nmd.2018.06.157

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CRISPR/Cas9 and TALEN edit the DMD genetic mutation in golden retriever muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a fatal childhood disease caused by mutations in the *DMD* gene that abolish the expression of dystrophin protein. Golden retriever muscular dystrophy (GRMD) is a naturally occurring, genetically homologous DMD model that closely recapitulates the progressive and variable phenotype seen in patients. A point mutation in the intron 6 DMD acceptor splice site in affected dogs disrupts the DMD reading frame, leading to exon 7 skipping, a stop codon in exon 8, and subsequent loss of dystrophin protein. In this study, we used clustered regularly interspaced short palindromic repeats (CRISPR) and transcription activator like effector nucleases (TALEN) to recover dystrophin expression via homology-directed repair (HDR) in GRMD dogs. We tested several single guide (sg)RNA combinations *in vitro*. After 70 hours of treatment in myoblasts followed by 3 weeks of differentiation into myotubes, the donor clone (with correct *DMD* gene sequence) was integrated into the GRMD DMD gene with both CRISPR/Cas-9 sgRNAs and TALEN arm treatments. There was a paradoxical decrease in DMD mRNA and an increase in dystrophin protein expression compared to non-treated GRMD cells. CRISPR/Cas-9 and donor clone were intramuscularly injected into the cranial tibial compartment (composed of three muscles) of a GRMD dog. Muscle was harvested 3 months post-injection and showed a respective 4% and 7% increase in dystrophin protein expression compared to saline-injected (3-month post injection) and baseline (pre-injection) GRMD muscle. These *in vitro* and *in vivo* results of the GRMD dog are consistent with previous findings of HDR-mediated gene editing in the mdx mouse model for DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.158

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AAV-mediated gene transfer with *GALGT2* in Duchenne muscular dystrophy: design of an ongoing phase I/II clinical trial

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Duchenne muscular dystrophy (DMD) is a severe, progressive, X-linked recessive neuromuscular disorder caused by mutations in the gene encoding the dystrophin protein. In its absence, components of the dystrophin-associated glycoprotein complex fail to anchor properly to the sarcolemmal membrane, resulting in chronic and progressive muscle damage and loss of

muscle function. The *GALGT2* gene encodes cytotoxic T cell (CT) βGalNAc transferase, an enzyme that produces the CT glycan on specific glycoproteins and glycolipids. *GALGT2* overexpression protects against muscle loss during eccentric contraction-induced injury in both healthy and dystrophic muscles, and may confer therapeutic benefit across numerous types of muscular dystrophies. In the mdx mouse model of DMD, transgenic or viral-mediated overexpression of *GALGT2* increases ectopic expression of synaptic binding proteins for dystroglycan (eg, utrophin) and inhibits the development of muscle pathology associated with muscular dystrophy. A phase 1/2, open-label dose escalation trial has been initiated to evaluate gene transfer of human *GALGT2* using the adeno-associated virus vector with MCK promoter (rAAVrh74.MCK.GALGT2) in DMD subjects. Using intravascular limb infusion, the *GALGT2* gene is delivered bilaterally to the legs via the femoral artery. The low dose cohort (n=3) receives the minimal efficacious dose predicted from preclinical studies (2.5e+13 vg/kg per leg, or 5e+13 vg/kg total), and the high dose cohort (n=3) receives 5e+13 vg/kg per leg (1e+14 vg/kg total). The primary objective of the study is safety and tolerability of the gene transfer. The primary efficacy outcome is expression of the CT glycan, measured by immunofluorescent staining of biopsies taken at baseline and at 3, 6, and 12 months. Secondary efficacy outcomes include assessments of motor function and limb MRI. The first patient received GALGT2 in December 2017, and we will present observations from the ongoing enrollment.

http://dx.doi.org/10.1016/j.nmd.2018.06.159

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Identification of developmental myosin positive fibres acts both as a clinical biomarker for muscle disease and an important component of the process to confirm ezutromid target engagement

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The expression of developmental and neonatal myosin heavy chains can be detected in newly formed regenerating skeletal myofibres 2-3 days after injury and remain for 2-3 weeks. These myosin isoforms are transiently expressed during regeneration and replaced when adult fast and slow myosins become prevalent. Therefore, the presence of developmental myosin heavy chain (MHCd) provides a very specific biomarker of regenerating fibres in pathologic skeletal muscle including DMD. Utrophin is also expressed in regenerating myofibres, following a similar restricted expression profile to MHCd. Summit have utilised novel automated immunohistochemistry imaging algorithms, in partnership with Flagship Biosciences, to quantify expression of developmental myosin heavy chain (MHCd) and utrophin in DMD patient muscle biopsies. This technology was utilised in the current Phase 2 open label study of ezutromid administered to 40 ambulatory patients with DMD where key secondary endpoints are from muscle biopsies; collected at baseline (n=40) and treatment Week 24 (n=25) or Week 48 (n=15). Compared to baseline, the Week 24 biopsies demonstrated a statistically significant decrease in the number of fibres expressing MHCd; the average reduction was -2.61% (95% CI -4.33, -0.90) from mean baseline of 11.37%; a relative reduction of 23%. This suggests a significant decrease in the number of fibres undergoing the natural repair process following damage. Additional functionality of the algorithms developed allows for assessment of expression heterogeneity across fibres and quantification of MHCd expression and utrophin expression in the same fibre. The individual fibre specific data analyses quantifying MHCd and utrophin comparing baseline to both Week 24 biopsies and Week 48 biopsies will be presented including those profiles that potentially distinguish a utrophin profile specific to ezutromid modulation.

http://dx.doi.org/10.1016/j.nmd.2018.06.160

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The burden of participation in a clinical trial for boys with Duchenne muscular dystrophy

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Despite some medical breakthroughs in Duchenne muscular dystrophy, no cure is available at this moment. New therapies are studied in clinical trials (CT)in boys with DMD. The investments of those boys and their families participating in CT may not be underestimated: time investment, impact on family activities, absence at work and school, side effects of the medication, systematic medical examinations,... There is a certain burden that comes with de participation to those trials, and studies investigating the impact of that burden are very scarce. The aim of this study is to develop an instrument to evaluate this burden and the impact of participation in a CT on the psychosocial wellbeing and quality of life of DMD boys and their parents. In a cross-sectional research design two groups of patients were asked to fulfill questionnaires. The first group were boys with DMD who participated in a CT. The control group consisted of age- and gender-matched boys with DMD. Parents of both groups were asked to answer a child Behavior Checklist (CBCL) reporting the psychosocial wellbeing of their child and an Adult Self Report (ASR) reflecting their own wellbeing. Moreover, they also received a pediatric quality of life inventory (PedsQL) to complete. The boys with DMD were asked to report their quality of life by completing an age appropriate version of the PedsQL. If they were older than 11 years an extra questionnaire was given, namely the Youth Self Report (YSR), reflecting their own wellbeing. To measure the burden of participation in a CT, a new instrument was developed: the Clinical Trial Survey (CTS). This survey includes 24 questions about different domains: demographic variables of the child, impact of participation in general, impact on employment of the parents, impact on school attendance of the children, impact on the relationship between the parents, and finally impact and experience of undergoing CT procedures. The CTS was only given to both parents of boys who participated to a CT. 25 children with DMD who participated in a CT were included. The control group consisted of 20 age-, gender- and disease-matched children. At this moment all questionnaires have been returned and are being processed. Definitive results are expected by the end of April.

http://dx.doi.org/10.1016/j.nmd.2018.06.161

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Comparing home-based respiratory function monitoring to hospital-based spirometry in Duchenne muscular dystrophy

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In Duchenne muscular dystrophy (DMD), respiratory function decline leads to a high disease burden and early mortality. Data comparing the similarity and reliability of home-based respiratory assessments to hospital-based spirometry assessments had been lacking. In DELOS, respiratory function data were prospectively collected from 64 DMD patients aged 10-18 years, not taking glucocorticoids. All patients had established respiratory function decline (defined as peak expiratory flow <80%p) at baseline, and were treated with idebenone (900 mg/day) or placebo. Hospital-based spirometry was conducted during hospital visits at baseline and at 3-month intervals thereafter over the 12-month study period. Patients also measured peak expiratory flow and forced expiratory volume in 1 second, expressed as percent of predicted (PEF%p, FEV1%p), weekly, at home, using the ASMA-1 device (Vitalograph). Data were analyzed using a mixed model for repeated measures. The mean age of DELOS participants was 14.3 years. A majority (92%) were non-ambulatory and showed signs of significant upper limb weakness at baseline (59% had a Brooke's score of ≥ 5). The weekly changes in PEF%p measured at home compared well with hospital-based measurements, showing a 5.6 ± 1.7% (95% CI, 2.16–9.04; p = 0.002) overall treatment difference from placebo in favor of idebenone across all weekly visits, compared to a

6.27% difference from placebo at last visit using standard hospital spirometry (95% CI, 0.61–11.93; p = 0.031). The weekly ASMA-1 data indicated a stabilization of PEF%p in the idebenone group versus a natural history-consistent decline in the placebo group – a result that was replicated by the hospital-based data. Home-based respiratory function monitoring is reliable in pediatric and adolescent patients with DMD, and may prove useful and convenient in combination with hospital-based monitoring. These data further support the efficacy of idebenone in slowing respiratory function decline in DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.162

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DMD-HUB: expanding clinical trial capacity for Duchenne muscular dystrophy, 1 year on

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The need to increase capacity for Duchenne muscular dystrophy (DMD) trials and improve trial readiness was identified. Specifically, clinicians in established UK clinical trial centres involved in multiple DMD studies were reaching capacity, while centers with capacity lacked the expertise and needed support to develop and achieve the requirements set by industry to run clinical trials. The DMD-Hub was set up as a unique partnership between Duchenne UK and two neuromuscular centres of excellence, The John Walton muscular dystrophy research centre in Newcastle and Great Ormond Street Institute of Child Health in London to address the issues together, share expertise and develop a network of trial ready centres able to take on interventional trials in DMD. Within the first year of operation the DMD-Hub launched two new Hub sites at Alder Hey and Leeds. In the second year three further trial sites at Glasgow, Bristol and Birmingham have received support and the DMD-Hub is working with additional sites (Oswestry, London, Cambridge and Manchester) to facilitate them taking on upcoming industry and academic led trials. Ongoing training and support for other sites is expected to open up additional opportunities in subsequent years. The DMD-Hub website (www.dmdhub.org) was also launched and is a key resource for industry, clinicians and patients. It hosts an interactive clinical trial finder detailing UK clinical trial opportunities for patients, includes a Toolkit containing training and educational material for sites and acts as a one-stop shop for industry / sponsors interested in conducting trials in the UK. Additional priorities for the second year include activating training programmes, expanding the Hub Toolkit and preparing for upcoming adult DMD trials. Innovative funding models are being implemented at DMD-Hub sites to ensure sustainability of the funded posts and expansion of the model to other rare neuromuscular diseases and other countries is being explored.

http://dx.doi.org/10.1016/j.nmd.2018.06.163

CONGENITAL MYOPATHIES (CNM)

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INCEPTUS pre-phase 1, prospective, non-interventional, natural history run-in study to evaluate subjects aged 3 years and younger with X-linked myotubular myopathy: preliminary findings

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XLMTM is a rare disease caused by mutations in the *MTM1* gene and characterized by profound muscle weakness, respiratory failure, and early death. INCEPTUS is a prospective, non-interventional study to evaluate XLMTM patients under 4 years of age. The objective is to characterize adverse events; neuromuscular, respiratory, and functional assessments; and to generate within-patient control data to support a Phase 1/2 gene therapy clinical trial (the ASPIRO study). 23 male patients (0.5-4.0 years of age) have been enrolled and followed with assessments every 3 months for up to 18 months. There have been 3 deaths and 38 serious adverse events, mainly due to respiratory tract infections. Neuromuscular function is severely compromised in this population, with high inter-patient variability: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) mean scores show a 4-point decline (baseline mean [SD, min-max]= 33.6 [8.4, 17-52] and month 12 mean= 29.6 [6.5, 19-40]). Motor Function Measure (MFM-20) mean scores show a 3.5% increase (baseline mean= 28.6% [16.0, 5-48.3] and month 12 mean= 31.5% [13.2, 11.7-50]). The majority of patients (n= 16/23, 69.6%) require invasive ventilatory support, many for 24h/day. Respiratory muscle strength measured as maximum inspiratory pressure (MIP, also referred to as Pimax) is low and mean scores show a 5.1 cmH2O decline (baseline mean= 33.6 cmH2O [15.2, 17.6-64.5] and month 12 mean= 28.5 cmH2O [8.35, 15.1-41.4]). Vocalization evaluations by handheld acoustic analyzer show no differences in loudness between talking and crying, further evidencing poor respiratory muscle strength. INCEPTUS data increase our understanding of respiratory issues and neuromuscular weakness in XLMTM and reinforce the severity and heterogeneity of the disease. The INCEPTUS study has additional operational value, as study sites build experience with the use of outcome measures also being used in ASPIRO.

http://dx.doi.org/10.1016/j.nmd.2018.06.164

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Novel deep intronic mutations in *MTM1* in X-linked myotubular myopathy

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X-Linked myotubular myopathy (XLMTM) is a congenital myopathy caused by mutations in *MTM1* gene encoding a 3-phosphoinositides phosphatase myotubularin. Typically, XLMTM patients clinically develop marked generalized hypotonia and muscle weakness with respiratory insufficiency since birth and pathologically show small-size fibers with peripheral halo and centrally-placed nuclei in the muscle. We performed RNA-seq screening on a cohort of 9 undiagnosed cases who were pathologically diagnosed as myotubular myopathy but had no mutation in exonic regions in *MTM1*. Sanger sequencing was performed to identify deep intronic mutation. We then performed *in vitro* splicing experiments using hybrid minigene plasmid H492 to evaluate splicing abnormalities. Retentions of intronic sequence were found in 2 patients; between exons 5 and 6 in patient 1 and between exons 11 and 12 in patient 2, respectively. These intronic exonizations are predicted to cause frameshift and subsequently create premature stop codon in both patients. Point mutations in deep introns were found: in intron 5 (c.343-1384 G>C) in patient 1 and in intron 11 (c.1261-647 C>G) in patient 2. The *in vitro* splicing experiments with artificial minigene constructs confirmed both of the deep intronic mutations exclusively produced abnormal splicing products. We report 2 novel point mutations in the deep introns in *MTM1*, both of which cause exonization of intronic sequences, introducing a premature stop codon, leading to XLMTM.

http://dx.doi.org/10.1016/j.nmd.2018.06.165

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The CHOP INTEND scale (Children's Hospital of Philadelphia infant test of neuromuscular disorders) in X-linked myotubular myopathy: content validity and psychometric performance

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XLMTM is a rare, congenital neuromuscular disorder characterized by extreme hypotonia, respiratory failure, and premature death. The CHOP INTEND is a measurement tool developed to assess motor function in patients with spinal muscular atrophy type I (SMAI), and successfully used in clinical trials to assess treatment response. As SMA I patients have a similar phenotype to infants with XLMTM, this study evaluated the CHOP INTEND as a measure of motor function in children with XLMTM. A literature review and qualitative interviews were completed (11 clinical experts, 5 caregivers); findings were used to determine content validity and develop a conceptual model of XLMTM, which were also assessed in a Delphi panel (7 clinical experts). Inter-rater reliability was evaluated among 15 physical therapists, with agreement between the ratings assessed based on independent review of videotaped assessments. The conceptual model of XLMTM includes body function and structural impairments (neuromuscular, pulmonary, musculoskeletal, gastrointestinal), as well as disease impacts (development skills, activities of daily living, caregiver burden). Concepts related to motor function map to most CHOP INTEND items. Caregiver descriptions of their child's function also align with items evaluated in the CHOP INTEND. The Delphi panel achieved consensus on the conceptual model of XLMTM and the appropriateness of the CHOP INTEND to assess motor function in XLMTM. Finally, the inter-rater reliability was supported with an intraclass correlation coefficient of 0.938 (95% CI: .902-.965). Results from this study suggest that the CHOP INTEND is a valid and reliable assessment tool for children with XLMTM, and support the appropriateness of its use in the ASPIRO gene therapy clinical trial as a co-primary endpoint. Next steps include evaluation of the psychometric performance of the CHOP INTEND in this population.

http://dx.doi.org/10.1016/j.nmd.2018.06.166

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Mortality and respiratory support in X-Linked myotubular myopathy: The RECENSUS Study, an international, multicenter, retrospective medical record review

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XLMTM is a rare, inherited myopathy caused by mutations in the *MTM1* gene resulting in severe hypotonia, weakness, respiratory failure, and early mortality. RECENSUS is an ongoing, international, multicenter, retrospective medical record review of male patients with XLMTM. The primary objective is to characterize disease manifestations and recorded medical management. In the current analysis of 136 patients, we describe mortality and respiratory support (RS). Data are described for the total cohort and the group that most closely matches the recently initiated ASPIRO gene therapy clinical trial (≤5 years old and RS at birth). Mortality among boys with genetically confirmed XLMTM was 44% overall, but 60% in patients ≤5 years old who required RS at birth. As a medical decision in line with perceived futility of treatment, life-sustaining therapy was withheld in 25/60 (42%) of patients with reported data. Respiratory failure was highly prevalent and was the cause of patient death in 23/37 (62%) of cases with documented information. Most patients (84%) required some form of RS at birth (54% received invasive RS, 24% non-invasive RS and 6% supplemental oxygen); of these, median time to death in those ≤5 years old was 2.2 years vs. 30.2 years in those >5 years old. Tracheostomies were placed at a mean age of 12.5 months overall and by 5.2 months in patients ≤5 years old who required RS at birth. Overall, tracheostomy-free survival decreased rapidly over time, and only 21% of patients who remained alive were tracheostomy-free by 4 years of age. Ventilator dependence >16 h/day was reported in 67/132 (51%) patients overall and 44/77 (57%) patients ≤5 years old who required RS at birth. The RECENSUS data show high mortality in young XLMTM patients despite RS and substantial disease burden (i.e. tracheostomy and ventilator use) in those who survive. These retrospective data support the significant unmet need in XLMTM patients ≤5 years of age, who are now the initial focus of the ASPIRO gene therapy trial.

http://dx.doi.org/10.1016/j.nmd.2018.06.167

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Clinical changes over time in a European and North-american cohort of patients with X-linked myotubular myopathy

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X-linked myotubular myopathy (XLMTM) is a rare neuromuscular disease with very heterogeneous clinical features varying from mild to severe with a death occurring in the first period of life mostly due to respiratory failure. Long term survivors with severe XLMTM remain often non-ambulant and need ventilation support. Less commonly, patients develop a mild phenotype, sometimes even starting during adulthood. Due to mutations in the *MTM1* gene located on the X-chromosome, the disorder predominantly affects males but female carriers can also develop symptoms. To insure clinical trial readiness in this population, we designed an international prospective and longitudinal natural history study in patients with XLMTM where muscle strength, motor function and respiratory function were assessed in a standardized manner at least every 6 months over the first year of follow-up. Forty-eight patients aged from 3.5 months to 56.8 years (45 males and 3 females) have been enrolled between May 2014 and May 2017. Forty patients were assessed over a 1-year period: 13 patients, including the 3 females, presented with a mild phenotype with no ventilation support needed, 10 presented with an intermediate phenotype (i.e. needing a ventilation support less than 12 hours a day) and 17 presented with a severe phenotype with a ventilation support more than 12 hours a day. Transversal data confirm that XLMTM is a very heterogeneous disease with a large phenotypic spectrum. Most of the assessments we selected could be performed even in very weak patients and discriminated well the three groups of patients. As expected, first analyses performed on longitudinal data confirm that, whatever the phenotype, respiratory, strength and motor function did not statistically decrease over a one-year period. Further analyses on variability and 2-years follow up data should permit to evaluate the most relevant endpoints for future clinical trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.168

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High frequency of manifesting carriers in the recessive X-linked myotubular myopathy

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Myotubular myopathy is a rare genetic disease which affects skeletal and respiratory muscles and it is caused by mutations in the *MTM1* gene. The disease is classified as a recessive X-linked inheritance and manifests in living born males with an estimated incidence of 1/50,000. Myotubular myopathy is characteristic and very severe, including hypotonia and generalized muscle weakness since birth. Most patients die in the first year of life due to respiratory failure. However, many cases with a more benign phenotype have recently been identified through molecular analysis. Women carrying the mutations are usually asymptomatic, but many cases of symptomatic heterozygous females have been reported, as compared with the lower frequency of manifesting carriers in other X-linked recessive diseases. Patients with structural congenital myopathies have been studied for more than twenty years at the human genome and stem cell research center (HUG-CELL) in Sao Paulo. Here, we have performed the molecular diagnosis of Brazilian families with myotubular myopathy, identified the female carriers of the families, and clinically evaluated their phenotype. Mutations in the *MTM1* gene were identified in patients from twelve different families, using a NGS panel for neuromuscular disorders. Seven among these mutations were novel. In two families, we identified 4/8 and 2/4 female carriers presenting some degree of clinical manifestation. A NGS exome study is ongoing to try to identify possible modifier genes to explain this clinical variability. Moreover, adding our cases with others presented in the international literature, we estimated the penetrance rate of the disease in 31.5% in females, which is compatible with a pattern of incomplete penetrance and could explain the higher frequency of manifesting women.

http://dx.doi.org/10.1016/j.nmd.2018.06.169

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X-linked myotubular myopathy with the presence of nemaline rods on muscle biopsy

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X-linked myotubular myopathy (XLMTM) is a rare muscular disorder with neonatal onset associated with severe hypotonia, weakness, respiratory failure, macrosomia and severe morbidity and mortality. It is classified as centronuclear myopathy based on pathologic description. The typical features include central nuclei in >25% of the fibers with abnormal oxidative stain distribution and type I atrophic fiber predominance. Here, we present a proband born from non-consanguineous parents with a neonatal presentation of severe muscle weakness, respiratory failure, mild ptosis, pectum excavatum and ischiotibialis muscle contraction. Care was withdrawn at 14 days of age. The muscle biopsy showed internalized nuclei, atrophic type I fibers, mild abnormal SDH staining and the presence of rods on Gömöri Trichome staining and in electron microscopy. An initial nemaline myopathy gene panel did not reveal any mutation in the known causative genes. An expanded neuromuscular panel including 117 genes, identified a de-novo mutation in *MTM1* c.1262G>A (p.Arg421Gln). This mutation has been previously reported, causing a disruption of the phosphatase domain. Since mutations in *MTM1* have not been previously associated with the presence of rods on muscle biopsy, we decided to analyze the transcriptome of the muscle, looking for non-coding mutations in the known nemaline myopathy genes. However extensive analysis did not identify any variants, novel junctions or transcript level abnormalities. In conclusion, we report a patient with a genetic diagnosis of XLMTM with a predominance of rods on muscle biopsy. Previous reports including this specific mutation did not describe rods on muscle biopsy. Possible explanations include the presence of modifier genes or a second gene mutation not yet associated with nemaline myopathy. Furthers studies will be needed for better understanding.

http://dx.doi.org/10.1016/j.nmd.2018.06.170

P.143

Myostatin as a novel blood based biomarker for antisense oligonucleotide-mediated Dnm2 knockdown to treat myotubular myopathy in mice

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Centronuclear myopathies (CNM) are non-dystrophic muscle diseases for which no effective therapy is currently available. The most severe form, X-linked CNM, is caused by myotubularin 1 (*MTM1*) loss-of-function mutations, while the main autosomal dominant form is due to dynamin2 (*DNM2*) mutations. We previously showed that genetic reduction of *DNM2* expression in *Mtm1* knockout (Mtm1KO) mice prevents development of muscle pathology. Most recently we have shown that weekly systemic delivery of Dnm2 antisense oligonucleotides (ASOs) into Mtm1KO mice efficiently reduces DNM2 protein level in muscle and prevents the myopathy from developing. In addition, systemic weekly ASO injection into severely affected mice leads to reversal of muscle pathology within two weeks. Here we perform a single injection of ASO into 3-week-old Mtm1KO mice, and complete clinical, histological and molecular analysis of the duration of the effects after a single injection. A single injection of 25mg/kg of ASO targeting *DNM2* increased the lifespan, whole body strength, and reduced disease severity in Mtm1KO mice compared to untreated controls. Despite these results, a single injection alone was not sufficient to rescue the disease for the lifespan of the mice, suggesting repeated treatments will be required. Thus, ASO-mediated *DNM2* knockdown can efficiently correct muscle defects due to loss of *MTM1*, providing an attractive therapeutic strategy for this disease. We next analyzed myostatin levels in muscles and blood of Mtm1KO mice. We show myostatin levels in plasma are significantly reduced in Mtm1KO mice, and that treatment by ASOs targeting *DNM2* significantly improves myostatin levels in plasma. In addition plasma myostatin levels inversely correlated with the level of DNM2 mRNA in muscles after injection with ASOs. This provides the first evidence of a blood based biomarker that can be used to monitor disease state and rescue in myotubular myopathy mice. With clinical trials for myotubular myopathy currently in progress, these results are of high relevance to the research field.

http://dx.doi.org/10.1016/j.nmd.2018.06.171

P.144

Targeting dynamin 2 rescues the three main forms of centronuclear myopathies

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Centronuclear myopathies (CNM) are a group of severe muscle diseases with no effective therapy currently available. The severe X-linked form of CNM is caused by loss-of-function mutations in myotubularin (*MTM1*), while 2 main autosomal forms are due to mutations in amphiphysin 2 (BIN1) or dynamin 2 (*DNM2*). We previously showed that reduction of *DNM2* by genetic cross in Mtm1KO mice rescues lifespan and prevents development of the skeletal muscle pathophysiology. This genetic proof-of-concept highlights epistasis between Mtm1 and Dnm2, and validates the concept of cross-therapy where downregulation of a CNM gene rescues loss of another CNM gene. However translation for therapeutic application requires a deliverable

compound. To this end we reduced *DNM2* expression using 2 different methods targeting Dnm2; single intramuscular injection of AAV-shRNA, or via weekly intraperitoneal delivery of antisense oligonucleotide (ASO) into Mtm1KO mice, which prevented the myopathy progression, and muscular mass, histology and force were corrected. We next investigated if the cross therapy approach could be applied to autosomal forms of CNM. While Bin1-/- mice die perinatally from a skeletal muscle defect, *Bin1-/-Dnm2+/-* mice survive at least 18 months, and have normal muscle force and intracellular organization of muscle fibers. These results indicate that BIN1 and DNM2 regulate muscle development, organization and function through a common pathway, and define BIN1 as a negative regulator of DNM2 *in vitro* and *in vivo* during muscle maturation. Finally we tested whether DNM2 reduction can rescue DNM2-related CNM in a knock-in mouse harboring the p.R465W mutation (Dnm2KI) displaying a mild CNM phenotype similar to patients with the same mutation. AAV-shRNA or antisense oligonucleotide (ASO) targeting both mutated and wild type *Dnm2* were administered to Dnm2KI mice from 3 weeks of age. Muscle mass, histopathology and muscle ultrastructure were indistinguishable from wildtype mice after reducing the total pool of DNM2. Here we therefore provide an example of treating a dominant disease by targeting both alleles, suggesting a novel strategy for other dominant diseases. Overall *DNM2* knockdown provides a common therapeutic strategy for several forms of centronuclear myopathies due to mutations in different genes. The next step will be to translate this strategy in CNM patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.172

P.145

Myotubular and centronuclear myopathy patient registry: accelerating the pace of research and treatment

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Myotubular and other centronuclear myopathies are congenital conditions characterised by the central location of the nucleus in the muscle cells. The most common form is the ultra-rare X-linked Myotubular Myopathy (XLMTM) with an estimated incidence of 1:50,000 male births. The myotubular and centronuclear myopathy (MTM & CNM) patient registry is an international, disease-specific, patient-reported registry collecting demographic, genetic and clinical data on living and deceased patients and female carriers of XLMTM. It aims to facilitate and accelerate clinical research through identification of participants and collection of information. On 3 April 2018 there were 228 participants from 34 countries. 190 had provided consent; of 140 living patients (113 male, 27 female), 26 female XLMTM carriers and 24 deceased patients (all male). Of the 140 living patients, 85 (61%) were diagnosed with myotubular myopathy and 36 (26%) with centronuclear myopathy. Genetic mutations were reported in the myotubularin gene (n=80), dynamin-2 (n=18), ryanodine receptor-1 (n=4), bridging integrator-1/amphiphysin-2 (n=2), and titin (n=1). The age range of living participants was 0-73 years, with a mean age of 19 years (living patients) and 46 years (female XLMTM carriers). 57% (n=80) of living patients used a wheelchair for all or some of the time, 39% (n=55) used invasive ventilation and 16% (n=23) used non-invasive ventilation. 49% (n=68) required ventilation at birth, and 51% (n=72) reported needing antibiotics for chest infections within the last 12 months. We observe heterogeneity in the clinical presentation; amongst female XLMTM carriers as well as patients with mutations in the same gene. The registry contains data from a diverse and growing international cohort. It has the potential to accelerate and support all areas of clinical research including trial feasibility and recruitment, outcome measures, understanding of phenotype-genotype correlation and improving standards of care.

http://dx.doi.org/10.1016/j.nmd.2018.06.173

P.146

Baseline characteristics of patients with centronuclear myopathy due to mutations in *DNM2* gene enrolled in a European prospective natural history study

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Centronuclear myopathy (CNM) is an inherited neuromuscular disorder characterized by the presence of hypotrophic myofibers with centrally placed nuclei on muscle biopsies. CNM exists in 3 forms: i) X-linked recessive caused by mutations in the *MTM1* gene (OMIM 310400), ii) autosomal dominant caused by mutations in the *DNM2* gene (OMIM 160150) and iii) autosomal recessive form due to mutations in the *BIN1* gene (OMIM 255200). In addition, mutations in other genes have been identified in some patients with clinicopathologic diagnosis compatible with CNM. Phenotype varies from mild to severe. The X-linked recessive form, called myotubular myopathy (XL-MTM), is the most severe form.

To insure clinical trial readiness in this population, we set up an international prospective and longitudinal natural history study where muscle strength, motor function and respiratory function were assessed in a standardized manner at least every 6 months over the first year of follow up. Forty-eight patients with XL-MTM have been enrolled between May 2014 and May 2017. This study was recently expanded to centronuclear myopathies due to mutations in *BIN1* and *DNM2* genes. Recruitment started on January 2018 and is planned to last 5 months. We present here the baseline data of the DNM2-CNM population by focusing on their motor development, upper limb strength, respiratory and motor function.

The data obtained will help to characterize the course of disease and the disease spectrum of CNM caused by mutation in *DNM2* gene and may help to empower future therapeutic studies as well as to eventually substitute for placebo groups.

http://dx.doi.org/10.1016/j.nmd.2018.06.174

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Novel SPEG mutations in congenital myopathy without centralized nuclei

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Congenital myopathies are clinically and genetically heterogeneous disorders characterized by distinctive morphological abnormalities in skeletal muscle fibers. Several genes have already been linked to congenital myopathies. However, about half of the patients do not have a genetic diagnosis. Within the 'Myocapture' project, a French consortium with the aim to better characterize the genetic data of patients, we studied a patient with molecularly unexplained muscle weakness. At birth, the patient presented with hypotonia and poor sucking. Motor milestones were delayed and cognitive involvement was normal. Reduced myocardial contraction appeared at age 5 and normalized with treatment. At 9 years of age, the patient presented with proximal and distal muscle weakness and facial weakness without ptosis. Morphological studies of muscle biopsy revealed mild fiber size heterogeneity as main histological change. Biallelic truncating SPEG mutations were identified by exome sequencing. *SPEG* encodes the striated muscle preferentially expressed protein kinase, that interacts with myotubularin (*MTM1*), a protein mutated in X-linked centronuclear myopathy (CNM). Biallelic *SPEG* mutations were recently described as mutated in patients with CNM associated in most cases with dilated cardiomyopathy. Conversely, in our patient, muscle biopsy did not reveal internalized nuclei and our patient did not develop dilated cardiomyopathy. Overall, we describe two novel SPEG mutations in a patient with a mild myopathy characterized by muscle weakness and fiber size heterogeneity on muscle biopsy. This study expands the spectrum of

diseases associated with mutations in *SPEG*, previously described in patients with CNM. Specific *SPEG* mutations can induce a severe CNM-like or, as described in our study, a rather moderate congenital myopathy without central nuclei.

http://dx.doi.org/10.1016/j.nmd.2018.06.175

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Centronuclear myopathy with BIN1-like myopathology and *DNM2* mutation

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A limited number of genetically proven cases of BIN1-CNM have been described. DNM2-CNM is more frequent and the main biopsy characteristics is fibers with radiating sarcomeric strands along with nuclear centralization. To present a Brazilian case of *DNM2* mutation and muscle biopsy with main features compatible with BIN1-CNM histopathology. Case report. A 58-year-old woman was born as a "weak child" with the "eyes closed". She had reduced spontaneous movements, delayed motor milestones and a motor limitation in follow other children in motor activities. Although motor weakness she was able to graduate in the university. Additional and more recent complains were hypersomnia and cognitive impairment. Consultation revealed: bilateral symmetrical ptosis and external ophthalmoplegia; motor deficit predominant at pelvic than scapular gilder; symmetric atrophy and weakness in distal lower limb. MFM scale had total score of 65.62% (D1=35.89%; D2=86.11%; D3=85.71%) and FVC was 32%. Recent Montreal cognitive assessment (MoCA) was 22/30. Cerebrospinal fluid showed protein of 82 mg/dL and Pandy positive. Biceps brachii biopsy showed several fibers with nuclear clustering centrally located and myofibers with one central nucleus. Type 1 fiber atrophy, type 2 hypertrophy and few fibers with radiating sarcomeric strands were also seen, thus predicting a CNM with *BIN1* mutation. Surprisingly muscle MRI was compatible with DNM2-CNM and a cerebral MRI disclosed meningioma. A panel of new generation sequencing for myopathies showed a pathogenic variant in Ch19:10.904.508C>T (c.1105C>T) diagnosing a DNM2-CNM related. After a successful neurosurgery, the patient never acquired spontaneous ventilation, as was suggestive by MFM and FVC, remained in intensive care unit for four months, had multiples episodes of septicemia and died. Our case expands histopathological phenotypes of DNM2-CNM and reinforce the features of pelvis and legs MRI in *DNM2* mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.176

INFLAMMATORY MYOPATHIES

P.149

Characterization of a cohort of Chinese inflammatory myopathy patients

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Idiopathic inflammatory myopathy is a group of acquired myopathies with subacute onset of limb muscle weakness. Here we describe the clinical and laboratory characteristics of 161 Chinese patients with inflammatory myopathies in Xiangya hospital from 2011 to 2017. Clinical and laboratory data were collected. Immunoassay for detection of myositis-specific antibodies was performed in 55 cases. Our cohort consisted of 70 patients with polymyositis (PM), 81 dermatomyositis (DM), 7 immune-mediated necrotizing myopathy (IMNM) and 3 inclusion body myositis (IBM). All four subtypes showed a tendency to affect female, which was most obvious in PM patients (1.69:1). The age of onset was as young as 6 and 3 years in our PM/DM patients respectively. In comparison, the disease presented in mid fortieth in IBM/IMNM. It took an average period of 10 months to reach a confirmative diagnosis for PM/DM patients, and 5.6 years for IBM. Dysphagia was present in a quarter of PM/DM patients and in as high as half of IMNM patients. Myalgia was found in 40-50% PM/DM/IMNM patients. Interestingly, the three IBM patients did not complain of dysphagia or myalgia. PM patients demonstrated the highest CK levels (mean±SD, 5037±4301U/L), whilst IBM the lowest (1108±1262U/L). In terms of myositis-specific antibodies (MSAs), Jo-1 antibody could be found in both PM and DM patients, and, together with other antisynthetase antibodies, are associated with interstitial lung disease (ILD, r=0.48). Ku, PL-7, PL-12, TIFγ, MDA5 and SAE antibodies could coexist with other MSAs, and isolated NXP antibody was found in a DM patient with profuse subcutaneous edema and respiratory failure. In contrast to previous studies, SRP antibody was found in combination with Ku in two PM patients. SRP antibody was found in 28% PM patients and 15% DM patients and 71.4% IMNM cases. Of interest, as much as 41.6% of these SRP positive cases also had ILD. In conclusion, apart from skin involvement and MSA profiles, patients with DM are clinically similar to those with PM in terms of gender preference, age of onset, muscle involvement pattern and disease progression, while IBM patients demonstrate a much later age of onset and a more mild clinical picture. ILD is associated with Jo-1 and other antisynthetase antibodies. In this cohort, a higher proportion of SRP positive patients also have ILD.

http://dx.doi.org/10.1016/j.nmd.2018.06.177

P.150

Clinical and muscle imaging follow-up in a cohort of patients with anti-SRP antibody myopathy

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Anti-signal recognition particle (SRP) antibody myopathy is an immune-mediated necrotizing myopathy characterized by severe progressive myopathy. We followed up a cohort of patients and analyzed the influencing factors related to therapeutic effect. Forty-eight patients were recruited including 14 males and 34 females. Patients performed the thigh MRI and muscle biopsy. We followed up the patients on 3, 6, 12, 18 and 24 months after treatment and divided them into refractory/non-refractory groups according to therapeutic effects. Results: The follow-up was completed in 40 out of 48 patients including 27 in non-refractory and 13 patients in refractory group. The mean onset age was 37.26 ± 18.06 years old in non-refractory and 50.77±15.77 in refractory group (p=0.029). The proportion of weight loss after disease onset was 40.7% for non-refractory and 76.9% for refractory group (p=0.032). Interstitial lung disease was 22.2% for non-refractory and 69.2% for refractory group (p=0.004). Thigh muscle MRI showed rapidly evolving infiltration in 29 (80.6%) and muscle edema in 32 (88.9%) patients before treatment. The average fatty infiltration score of adductor magnus was 1.00 and 2.06 respectively in non-refractory and refractory group (p=0.028). The average edema score of adductor magnus was 3.80 and 2.29 respectively in the two groups (Pp=0.028). The average edema score of biceps femoris was 3.80 and 2.35 in the two groups (p=0.041). The mean fatty infiltration rate was 2.38 for non-refractory group and 5.55 for refractory group during thigh MRI follow-up (p=0.022). Male, severe muscle weakness and interstitial lung disease were independent risk factors for refractory patients in binary logistic regression analysis ($p < 0.05$). Male, late disease onset, weight loss, severe muscle weakness, interstitial lung disease were risk factors to therapy refractoriness. Quick fatty infiltration in thigh also indicated poor response for therapy.

http://dx.doi.org/10.1016/j.nmd.2018.06.178

P.151

Spontaneous recovery in a child with anti- HMGCR autoimmune necrotizing myopathy

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Antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) have recently been associated with immune-mediated necrotizing myopathy (IMNM), a subgroup of idiopathic inflammatory myopathies (IIMs). Most patients require long term immunomodulatory therapy for remission and only a few cases of spontaneous improvement in adults have been reported. We present a six-year-old Chilean girl, with an anti- HMGCR IMNM initially diagnosed with muscular dystrophy. At the age of 4, she had a subacute onset of progressive proximal weakness with high CK level (7.842 U/L), muscle biopsy with a dystrophic pattern, normal immunohistochemical labeling for membrane sarcolemmal proteins and no inflammatory infiltrates. NGS panel for muscular dystrophy and Pompe disease was negative. Ten months after symptomś onset, she developed spontaneous improvement of strength, reaching near-full capacity for daily activities and climbing stairs without support objectified by the Expanded Hammersmith Functional Motor Scale (HFMSE) and CK decline levels. High levels of anti-HMGCR (> 200) drove us to establish an anti-HMGCR IMNM as her definitive diagnosis. Clinical observation was done at first, but after a six months follow-up, she reached a clinical plateau, remaining with slight residual proximal limb weakness and mild cervical weakness. She received one pulse of IV-Ig treatment (2 gr/kg IV) reaching maximal strength (HFMSE 66/66), which has maintained after ten months follow-up. This clinical report shows that spontaneous remission can occur in pediatric IMNM patients and that the phenotypic spectrum remains to be fully described. The lack of information about the natural evolution of the disease precludes the elaboration of a treatment algorithm. It is crucial to define groups of better prognosis like this case, in whom less aggressive treatment can be done at the beginning, avoiding long-term adverse effects of steroidal and immunomodulatory therapies.

http://dx.doi.org/10.1016/j.nmd.2018.06.179

P.152

Early-onset anti-HMGCR myopathy associated with muscle mitochondrial alterations and calpain-3 deficiency

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Immune-mediated necrotizing myopathy (IMNM) associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) autoantibodies have been described in pediatric patients without history of statins intake. Patients presented with a subacute-onset myopathy and a biopsy consistent with an IMNM. We report on a 20 year-old Italian patient who presented at age 11 with progressive scapular winging, and proximal weakness of both upper and lower limbs. A clinical assessment at 19 years showed high-arched palate and asymmetric scapular atrophy and winging, mild cyphoscoliosis and thoraco-lumbar rigidity. There was upper limb girdle muscle weakness quoting 3/4 MRC with triceps sparing, and lower limb girdle muscle weakness quoting 4. Axial weakness involved neck flexor and abdominal muscles. Serum CK were repeatedly elevated, up to 9000 UI/l. Serum anti-HMGCR were 177 U/ml (normal $\leq$ 20U/ml). Cardiac and respiratory workup were normal. A vastus lateralis muscle biopsy at 17 years showed rare necrotic fibers. A deltoid muscle biopsy at 19 years showed necrotizing myopathy, numerous ragged-red fibers, and pale COX histoenzymatic reaction with several COX- fibers. MCH-1 was expressed at the membrane of all muscle fibers. There was sarcolemmal deposition of C5b-9 in few fibers. Muscle multiplex Western Blot revealed severe 94 Kda and 30 Kda calpain-3 reduction. Acid maltase, FSHD1, and targeted NGS for LGMDs associated genes including *CAPN3*, failed to reveal genetic variants potentially associated with the disease. The patient received corticosteroid and intermittent IVIg therapy with partial and non-consistent amelioration of muscle strength and serum CK reduction. A recent myopathological study conducted in three muscle biopsies from adult HMGCR-myopathy patients revealed mitochondrial changes and sign of mitophagy. On the other hand, *CAPN3* is known to be a regulator of mitochondrial function causing oxidative/nitrosative stress-induced damage in skeletal muscle of LGMD2A patents. In conclusion, we describe a young patient with anti-HMGCR myopathy showing muscle mitochondrial alterations and *CAPN3* deficiency suggesting a possible role of oxidatoxidative nitrosative stress in the pathogenesis of muscle degeneration in anti-HMGCR myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.180

P.153

Tight association between microinfarction and capillary MAC deposition in dermatomyositis

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Microinfarction (MI) is a pathological phenomenon related to dermatomyositis (DM). Nevertheless, clinicopathological characteristics of DM with MI are largely unknown. We defined microinfaction by the absence of oxidative enzyme activity on NADH-TR in a cluster of at least 20 muscle fibers. Then we surveyed all cases whose myopathological diagnosis was made at our center and reviewed the clinicopathological data of cases with MI. Among 18113 cases whose pathological diagnosis was made in NCNP on July 1978 through March 2018, 521 cases were diagnosed as DM (56 pediatric and 465 adult patients). Among them, MI was observed in 27 (5%) patients (27% [15/56] in children and 3% [12/465] in adults). Clinically, all showed subacute muscle weakness (3.2±3.0 months before muscle biopsy) and 67% (18/27) had rash typical of DM. CK was elevated to 3144±4074 U/l (pediatric: 3994±5083 U/l, adult: 2165±2037 U/l) but was normal in 3 children. Pathologically, perifascicular atrophy, MAC deposition in capillaries and MxA expression on myofibers were seen respectively in 63% (17/27: 11 pediatric and 6 adult), 100% and 100% of patients with MI but in 56% (278/494), 73% (88/120) and 99% (159/160) of those without MI. Autoantibodies to NXP2, MDA5 and TIF1-γ were respectively found in 2 children, 2 children and 1 adult, and 1 adult DM patients. MI is seen in 27% of DM in children, but in only 3% of DM in adults. Capillary MAC deposition is highly associated with MI (all cases in this study), suggesting a causal relationship between vasculopathy and MI. MxA immunohistochemistry is useful in the diagnosis of DM also in cases with MI.

http://dx.doi.org/10.1016/j.nmd.2018.06.181

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Brachio-cervical myopathy as the clinical presentation of scleroderma. Case series

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Brachio-cervical weakness can be the presenting symptom of several neuromuscular disorders. It's more frequently associated to amyotrophic lateral sclerosis or myasthenia gravis, and there are very few reports about inflammatory myopathies. These reports link inflammatory myopathies to other autoimmune disorders. It's imperative to consider this entity because a correct diagnosis has important implications for treatment. We describe 6 patients (5 women) with brachio-cervical myopathy associated to Scleroderma. All of them began to have arm or neck weakness at an average age of 45.7 years-old (27-61). The time from the onset of symptoms to diagnosis varied from 6 months to 3 years. All of them had associated bulbar symptoms. They were later diagnosed with Scleroderma. 5 of them had ANA antibodies (one ACA-B, one SSA/Ro, two Th/To and one anti-Ku and anti-Mi2). Capillaroscopy showed an active scleroderma pattern in all patients. 5 had esophagus aperistalsis or dilation. 4 had associated lung disease. All of them had a normal echocardiography. Muscle biopsies showed unspecific myopathic

changes along with increased expression of MHC class I and a variable degree of macrophage infiltration. Some biopsies showed other findings such as CD20, CD4 and CD8 infiltrates and neurogenic changes. All our patients were treated with immunosuppressant drugs. One patient died of respiratory failure after 20 months of intense therapy. The other 5 have shown partial response and stabilization of the disease. In our case series, in younger patients the disease progressed more slowly over several years and was initially misdiagnosed as a muscle dystrophy. Capillaroscopy was pathological in all cases, even those who didn't have Raynaud syndrome. Although the SSc-PM overlap syndrome has been strongly associated to myocardial disease, none of our patients had myocardiopathy. None of them presented PM-Scl antibodies either. Brachio-cervical weakness can be a presenting symptom of inflammatory myopathy associated to scleroderma. In cases of proximal upper limb weakness or dropped head we should look for signs of systemic involvement. Capillaroscopy is an efficient and useful tool for diagnosis. Patients with this phenotype might have distinctive characteristics such as myocardial sparing.

http://dx.doi.org/10.1016/j.nmd.2018.06.183

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Brachio-cervical inflammatory myopathy with lymphoid follicle-like structures in a patient with scleroderma

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Ectopic lymphoid follicle may be found in connective tissue diseases and has been reported in lupus panniculitis, erythema nodosum, subcutaneous tissue in patients with scleroderma, and, recently, in the muscle of patients with dermatomyositis and brachio-cervical inflammatory myopathy. We report a patient with clinical scleroderma presenting with subacute myopathy with lymphoid follicle on muscle histology. A 29-year-old female with scleroderma confirmed by clinical criteria and skin biopsy, using colchicine, presented with subacute proximal muscle weakness associated with dysphagia and dropped head without CK elevation, but EMG/NCS demonstrated myopathic findings. Her neurological examination revealed symmetrical muscle weakness, MRC 2 in deltoid and cervical muscles and MRC 4 in the other proximal muscles in the upper and lower extremities (brachio-cervical phenotype). Muscle contrast-enhanced MRI (T1) revealed areas of hyperintensity with diffuse gadolinium uptake in the affected muscles, involving fascia and subcutaneous layers of proximal aspect of upper limbs and cervical extensor muscles. Brachio-cervical inflammatory myopathy was considered and the patient underwent a left deltoid muscle biopsy that showed a dystrophic pattern with granulomatous inflammation that was compatible with lymphoid follicle-like structures, rich in B-cells. The patient was treated with prednisone and chloroquine, without complete improvement and is still in follow-up. We showed a very unusual case of brachio-cervical inflammatory myopathy with lymphoid follicle-like structures in a patient with scleroderma, which expands the spectrum of muscle involvement of this disease. There is only one case previously published in literature that demonstrates this association.

http://dx.doi.org/10.1016/j.nmd.2018.06.184

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Dysfunctional T cells in immune mediated necrotizing myopathy, inclusion body myopathy and immune toxicity related myopathy

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Chronic exposure to antigens in immune-mediated necrotizing myopathies (IMNM) and sporadic inclusion body myopathy (sIBM) may lead to T cell exhaustion. This process in which T cell function is deteriorated is controlled by the programmed cell death protein 1 (PD1) receptor and its cognate ligands PD-L1/PD-L2. Blocking these molecules using immune checkpoint inhibitors (ICI) improves the outcome of several cancers. However, therapy with ICIs may lead to increased autoimmune responses with development of myositis or myocarditis, highlighting the relevance of this pathway in muscle inflammation. We previously showed that T cells lack robust cytotoxicity in IMNM as opposed to sIBM. Here, we analyse T cell exhaustion and senescence in skeletal muscle biopsies from IMNM and sIBM, as well as from patients treated with myositis triggered by treatment with ICIs (irMyositis). $CD3^+CD8^+$ T cells were largely PD1-positive in IMNM, sIBM and irMyositis, while $CD68^+$ macrophages were weakly PD-L1- positive. The sarcolemma of myofibers was $PD\text{-}L2^+$ and co-localized with MHC class I. $CD68^+$ macrophages co-localized with PD-L2. Senescent T cells, expressing CD57, KLRG1, TBX21, were strongly enriched in skeletal muscle of sIBM. Patients with irMyositis showed mild signs of senescence and exhaustion. These data highlight the relevance of T-cell exhaustion and the PD-1 pathway in IMNM, sIBM and irMyositis.

http://dx.doi.org/10.1016/j.nmd.2018.06.185

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$Kv1.3^+$ cells in blood and muscle from patients with sporadic inclusion body myositis

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To evaluate circulating $Kv1.3^+$ cells in patients with sporadic inclusion body myositis (sIBM) and other inflammatory myopathies. We had recently shown that muscle biopsies from patients with sIBM express large numbers of $CD3^+$ cells (22.4% to 53.1%) that co-localized Kv1.3, a voltage-gated potassium channel seen on effector memory T-cells. We examined if circulating $Kv1.3^+$ cells can be detected in unstimulated samples from sIBM patients. Blood collection was done at the annual patient conference of the Myositis Association in San Diego, CA with immediate processing for PBMCs. Multichannel flow cytometry was done, with a panel containing the following markers: CD3, CD8, CD4, CD244, CD57, CD28 viability marker, and Kv1.3. Descriptive statistics and student t-tests were used for statistical purposes. PBMCs were collected from 22 patients with a diagnosis of IBM, 9 patients with PM, 9 patients with DM and 5 healthy controls. $CD4^+CD57^+CD28$null cells were seen in 3.8 0.9% of sIBM patients ($p=0.02$ vs. HC) while $CD8^+CD57^+CD28$null cells were seen in 50 3.6% of sIBM patients ($p=0.01$ vs. HC). The percentage of these cells was not statistically different in DM and PM patients. Percentage of $Kv1.3^+$ cells was statistically increased in both $CD4^+$ as well as $CD8^+$ cell populations ($CD4^+CD244^+Kv1.3^+ = 0.53$ 0.15%; $p<0.02$ vs HC and $CD8^+CD244^+Kv1.3^+ = 1.70$ 0.21%; $p=0.02$). Circulating $Kv1.3^+$ cells were statistically increased in sIBM compared to healthy controls and other inflammatory myopathies. The numbers of these cells are small, probably representing a small percentage of the large T-cell repertoire in circulating blood. We are working on isolating live T-cells from skeletal muscle biopsies from sIBM patients to quantitate presence of $Kv1.3^+$ cells in diseased muscles and will present this data.

http://dx.doi.org/10.1016/j.nmd.2018.06.186

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Feasibility and validation of modified oculobulbar facial respiratory score (mOBFRS) in sporadic inclusion body myositis

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Sporadic inclusion body myositis (sIBM) is a neurodegenerative disorder that results in progressive limb muscle weakness with bulbar and respiratory involvement. The leading cause of morbidity and mortality are secondary to bulbar dysfunction. The IBMFRS is a reliable patient reported outcome measure used in sIBM, however, we lack objective scales that can quantitate dete-

rioration in bulbar and respiratory functions. We are conducting a prospective study to test the feasibility of using, and validate the use of the modified oculobulbar facial respiratory score (mOBFRS) in sIBM. The mOBFRS is validated in immune myasthenia gravis. We will evaluate if changes in mOBFRS in sIBM: 1) can be reliably measured on a serial basis; 2) correlate with scores of the existing subjective IBM Functional Rating Scale (IBMFRS) and objective Bulbar Rating Scale (BRS); and 3) can be used as a potential outcome measure in clinical trials. Subjects are tested at baseline, month 6 and month 12. Interim analysis was done using a linear mixed effect model to assess the BRS compared with mOBFRS as fixed effect and a random intercept to account for the with-in subject correlation. Pearson's correlation was calculated between swallow time and subjective swallow ability at each visit. Within the first 12 months 36 subjects have completed visit one, 19 completed month 6, and 4 completed month 12. The mOBFRS score is significantly associated with the BRS along all three visits ($p < 0.0001$). One score change of mOBFRS leads to an average of 0.39 point change in the BRS. The IBMFRS swallow ability question was compared to the mOBFRS timed swallow test which showed no correlation at any of the three visits. Conducting the mOBFRS in a clinic setting has proved to be feasible. mOBFRS is trending to be a useful measure of bulbar function but the study is ongoing.

http://dx.doi.org/10.1016/j.nmd.2018.06.187

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A bioinformatics approach to define the aggregation capacity of the myofiber proteome in inclusion body myositis

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The aggregation and accumulation of proteins is a pathologic feature of proteinopathies, including hereditary myopathies such as myofibrillar myopathies (MFMs) and acquired disorders such as sporadic inclusion body myositis (sIBM). In some dominantly inherited proteinopathies a pathogenic protein has a destabilizing mutation that results in its aggregation within affected tissue, generating a protein aggregate. Alternatively, a mutation within a component of the protein homeostatic machinery (i.e. chaperone) leads to impaired protein folding and subsequent aggregation within the affected tissue. In acquired proteinopathies such as sIBM, the aggregation and accumulation of misfolded proteins is less clear but may relate to a reduction in the proteostatic capacity of the tissue resulting in inclusion body formation. We utilized individual patient derived proteomic datasets from MFM and sIBM biopsies that included both inclusion and non-inclusion bearing fibers to compare the aggregation propensity and concentration of aggregate proteins as a proxy for the biophysical state of the myofiber proteome. Our analysis finds that the burden of a metastable aggregate proteome is apparent in unaffected patient tissue. Moreover, this burden increase as samples are taken more proximal to the pathologic inclusion. Inclusion bearing myofibers downregulate a subset of proteins that are themselves inherently aggregation prone yet the aggregate proteome escapes this regulation depositing as pathologic inclusions. With the use of human tissue and proteomic analysis, this study reveals a potential common pathogenic mechanism that relates hereditary and acquired protein aggregate myopathies.

http://dx.doi.org/10.1016/j.nmd.2018.06.188

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A rare case of distal myositis in a patient with thymoma

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There have been several reports of patients with both myasthenia gravis (MG) and inflammatory myositis. Thymic pathology may be contribute to the pathogenesis. We herein describe a patient with distal myositis associated with thymoma, but not accompanied by MG symptom. A 54-year-old man presented with bilateral hands weakness and frequent cramps since 5 weeks ago. Subsequently, generalized myalgia and gait disturbance had developed over several days. Neurological examination revealed symmetric distal dominant weakness in the bilateral upper extremity; however, sensory impairment was not observed. Severe atrophy of the bilateral first dorsal interossei and thenar muscles was noted, and the patient had lost 8 kg over 10 days. The level of serum creatine kinase was elevated at 7431 IU/L and acetylcholine receptor antibody was positive (5.82 nmol/L). Anti-Jo 1 antibody was not detected. The results of nerve conduction study and needle electromyography were compatible with active myopathy. Repetitive nerve stimulation test did not show decremental response on any muscle. Chest computed tomography demonstrated 6.8 cm sized heterogeneously enhancing lobulated mass with internal calcification in the anterior mediastinum. Total thymectomy was done and type B2 thymoma was confirmed. The results of muscle biopsy showed chronic granulomatous and suppurative inflammation with marked neutrophil infiltration which is consistent with thymoma-associated granulomatous myositis. Intravenous methylprednisolone was initiated, and muscle weakness of the patient was much improved. We report a case of thymoma-associated distal myositis which is extremely rare. Thymoma may be associated with diverse neuromuscular disorders including inflammatory myopathy and peripheral neuropathy as well as MG.

http://dx.doi.org/10.1016/j.nmd.2018.06.189

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IgG-4 related myositis - a new entity among inflammatory myopathies

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IgG4-related diseases (IgG4RD) are exceedingly rare, have only been recently discovered and the nosological spectrum is only beginning to be understood. Affected patients suffer from subacute non-specific general complaints often associated with organ-specific affection typically of the salivary or lacrimal glands, formation of so-called pseudo-tumours with fibrous characteristics, and interestingly often multi-organ affections. Gold standard for diagnosis of IgG4RD is the histopathological analysis, highlighting the characteristic lymphocytoplasmic infiltrates, storiform fibrosis and obliterative phlebitis in combination with IgG4-positive Plasma cells. We present a 55-year-old female patient with a 30-year history of atypical rheumatoid arthritis suffering from a 12-year history of axial muscle weakness including paravertebral muscles. No other organs were involved. Her laboratory markers included eosinophilia, elevated soluble IL-2 receptor and IgG4. On muscle biopsy an unusually dense lymphomonocytic infiltrate including numerous Eosinophils and Giant cells as well as numerous IgG4-positive plasma cells were detectable. In general, IgG4-RD responds well to treatment, especially to B cell depletion, however our patient did not. As a second-line treatment, she received a JAK1 and JAK2 inhibitor, which dramatically improved her muscle strength over a 3 months period. This report highlights that myositis can be the sole presentation of IgG4 related disease and that treatment may require alternative approaches, which in turn open speculations about pathophysiological underpinnings of the disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.190

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Myositis and fasciitis due to disseminated histoplasmosis

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TNFα inhibitors affect host resistance to granulomatous diseases. We present the case of a patient with rheumatoid arthritis (RA) on etanercept

who presented with panniculitis and myositis and fasciitis due to histoplammosis. Case report. A 53-year-old female with rheumatoid arthritis, using methotrexate and etanercept, was admitted to our service due to high fever, pain, redness and swollen in the right upper limb and right thigh. She denied any pulmonary symptoms. Physical examination showed diffuse erythema and edema on the right forearm and arm and right thigh with local heat and palpation pain. Laboratory tests showed high C-reactive protein (20.9 mg/dL) and normal CK level (129 U/L). Aerobic and anaerobic blood culture were negative. Serologies for HIV and hepatitis B and C viruses were all negative. Transesophageal echocardiography, thoracic and abdominal computed tomography were normal. Empiric treatment for bacterial cellulitis with cefuroxime, menopenem, linezolid, and polymyxin-B, was not effective and clinical worsening was observed. Muscle MRI of the right forearm and thighs depicted a high intensity signal on STIR, indicating oedema in the forearm extensor compartment and in the posterior compartment of the right thigh with edema in the myofascial planes and subcutaneous tissue. A muscle biopsy revealed intense endomysial and perimysial inflammatory reaction and Grocott methenamine silver staining showed intracellular, oval shaped organisms compatible with H. capsulatum. She was treated with amphotericin and itraconazole, presenting progressive and complete improvement. Discussion. Disseminated histoplasmosis may rarely present as myositis and fasciitis. We highlight the presence of panniculitis on the image as a clinical key to consider this etiology. Specific staining to H. capsulatum might be performed on muscle specimen in the setting of focal inflammatory myopathy, especially if the fascia and subcutaneous tissue are involved.

http://dx.doi.org/10.1016/j.nmd.2018.06.191

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Predictive value of cerebral 18F-FDG PET for diagnosing macrophagic myofasciitis: an individual SVM-based approach

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Macrophagic myofasciitis (MMF) is a condition characterized by a clinical triad including chronic fatigue, myalgias and cognitive impairment, associated with highly specific myopathological alterations. A peculiar spatial pattern of a cerebral glucose hypometabolism involving occipito-temporal cortex and cerebellum have been reported in patients with MMF; however, the full pattern is not systematically present in routine interpretation of scans, and with varying degrees of severity depending on the cognitive profile of patients. We aimed to generate and evaluate a support vector machine (SVM) procedure to classify patients between healthy or MMF 18F-FDG brain profiles. 18F-FDG PET brain images of 119 patients with MMF and 64 healthy subjects were retrospectively analyzed. The whole-population was divided into two groups; a training set (100 MMF, 44 healthy subjects) and a testing set (19 MMF, 20 healthy subjects). Dimensionality reduction was performed using a t-map from statistical parametric mapping (SPM) and a SVM with a linear kernel was trained on the training set. To evaluate the performance of the SVM classifier, values of sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy (Acc) were calculated. The SPM12 analysis on the training set exhibited the already reported hypometabolism pattern involving occipito-temporal and fronto-parietal cortices, limbic system and cerebellum. The SVM procedure, based on the t-test mask generated from the training set, correctly classified MMF patients of the testing set with following Se, Sp, PPV, NPV and Acc: 89%, 85%, 85%, 89%, and 87%. We developed an original and individual approach including a SVM to classify patients between healthy or MMF metabolic brain profiles using 18F-FDG-PET. Machine learning algorithms are promising for computer-aided diagnosis but will need further validation in prospective cohorts.

http://dx.doi.org/10.1016/j.nmd.2018.06.192

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Sporadic late-onset Nemaline myopathy

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Sporadic late-onset nemaline myopathy (SLONM) is a rare disease that can be associated with a monoclonal gammopathy (MG) or HIV infection. The diagnosis remains challenging and little is known about optimal treatment or long-term outcomes. We collected clinical and laboratory data of SLONM patients seen at our institution between 2000 and 2017. Treatment response was classified as mild, moderate, or marked as adjudged by predefined criteria based on improvement of muscle strength, cardiac and pulmonary function, and activity of daily living.We identified 28 patients: 18 with MG and 10 without, none with HIV. Median age at diagnosis was 61.5 years. The MG was always an IgG, 50% lambda subtype. Survival rate from symptom onset was 91% at 5 years and 64% at 10 years; there was no difference among patients with and without MG. Treatment follow-up was available on fifteen patients, with a median of 34 months (range 9-124) from presentation to our institution. Treatments were as follows: 10 patients received IVIG-based therapy, 8 plasma-cell directed therapy (PCDT) (of which 6 autologous stem cell transplant-ASCT and 2 lenalidomide-based therapy) and 8 other immunosuppressive therapies (IST). Responses were as follows: 8/10 (80%) patients responded to IVIG (marked improvement: n=3 of which 2 had an associated MG, moderate: n=2, and mild: n=3); 6/8 (80%) patients responded to PCDT (moderate improvement: n=3, mild: n=3) and one patient responded to IST (azathioprine), p=0.02. Median time to neurologic progression was not reached for IVIG and PCDT vs 37 months for IST (p=0.09). The survival of patients with SLONM in this contemporary cohort appears better than previously reported irrespective of the presence of MGUS. IVIG is associated with good outcomes and should be considered in all patients. PCDT is a reasonable second line therapy for patients with an associated MGUS. The advantage of ASCT over less aggressive PCDT remains unclear.

http://dx.doi.org/10.1016/j.nmd.2018.06.193

SMA THERAPIES I

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Evaluating the respiratory health of children with spinal muscular atrophy type 1 on nusinersen under the Expanded Access Program (EAP)

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Nusinersen (Spinraza) (NUS) is the first treatment approved for SMA and is currently only available in the UK for SMA1 recruited in the EAP. Studies have reported improvement in motor function with limited data on respiratory assessment. The Great Ormond Street Respiratory (GSR) score was developed as an objective respiratory assessment tool for children with SMA1 during their treatment with NUS. The score (1-26) takes into account SMA1 subtypes, needs for physiotherapy and non-invasive ventilation (NIV). (1) To track the respiratory status of SMA1 children over the course of NUS treatment; (2) To compare the GSR scores of SMA1 sub-types. SMA1 patients were assessed using the GSR score at set time points: prior to first NUS dose; 2 weeks post 4th dose (end of loading doses); 2 weeks post-subsequent doses. GSR score interpretation: 1-9 = Stable minimal support; 10-15 = Stable with Cough Assist (MIE) and physio; 16-21= Stable with NIV and MIE; 22-26 = Poor reserve with maximum support. Results: 18 SMA1 children (7 males; 11 females), underwent NUS treatment. The median age of diagnosis is 6.8 (IQR 3-9.5) months. NUS was started at median of 10.2 (IQR 4.5-21.6) months. The median GSR [IQR] scores were: 6.5 [2.8-17.3] prior to 1st dose; 16 ([6.5-20.8] post 4th dose; 17.5 [12-21] post 5th dose; 17.0 [9-23.3] post 6th dose. By 5th and 6th dose, GSR scores were significantly lower for Type 1c patients (n=10) compared to Type 1b patients

(n=8) - 5th dose: Type1b 21 [18.5-23] vs Type 1c 11 [5-16] (p=0.02); 6th dose: Type 1b 22.5 [20.3-24.8] vs Type1c 10 [6.5-13.5],(p=0.02). Based on the GSR scores, our SMA1 cohort on NUS therapy did not show significant improvement in respiratory health in the initial phase of treatment. By 5th and 6th dose, a significant difference in GSR score emerged between SMA 1b and 1c patients. Further longitudinal study is needed to chart the effect of NUS on motor and respiratory functions amongst SMA1 patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.195

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Treatment by nusinersen in spinal muscular atrophy type 1 patients older than 7 months: 14 months follow-up

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We previously showed that treatment by nusinersen in spinal muscular atrophy (SMA) type 1 patients older than 7 months may have comparable effects to those observed in the younger population, but the response to the treatment is highly variable. In our cohort, median improvement in the modified motor milestones Hammersmith infant neurological exam (HINE-2) score was 1.5 points after 6 months of treatment and 2 points after 10 months. We still lack long-term clinical data and predictive factors for clinical benefit in this cohort. We present 14-months' follow-up data (corresponding to 7 injections of nusinersen) of 40 patients with SMA type 1 (21 boys and 19 girls) treated by nusinersen at the median age of 22 months (8.3-113). Patients' data are recorded in an ERB-approved registry (NCT03339830) at the following time points – before treatment, at two months of treatment (end of the loading dose) and at each injection every 4 months subsequently. Our analysis will focus on the level of respiratory and nutritional support, and on the motor function assessed by the HINE-2 evaluation. We will test the correlation between the HINE-2 score changes after 14 months of treatment and the scores before treatment, after two and after six months of treatment. We will also study the influence of the age at the beginning of the treatment and of the *SMN2* copies status on the Hine-2 changes at month 14. The objective of this work is to present longitudinal data and to pre-identify predictive factors for the 14 months clinical benefit of nusinersen treatment in SMA type 1 patients older than 7 months.

http://dx.doi.org/10.1016/j.nmd.2018.06.196

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Nusinersen experience in spinal muscular atrophy type 1: two-year results of 21 patients

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Spinal muscular atrophy (SMA) is a genetically programmed loss of the anterior horn motor cell. The *SMN1* gene located in the 5q region is often seen with homozygous deletion with autosomal recessive origin. The SMN2 gene in this genome can produce 10-15% protein. The principle of antisense oligonucleotide therapy is based on avoiding alternative splicing by retaining exon 7 in the *SMN2* gene. As a result, protein synthesis will increase an additional 10-15%. Nusinersen is one of the earliest examples of this targeted, intrathecal way of applying medicine to an individual. In our study, the results of 2 years follow-up of 21 babies / children in different age groups and different treatment programs were examined. The starting age of treatment ranged from 4 days to 10.5 years. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) was administered one day before intrathecal administration to determine the level of functional benefit. The mean age of 21 babies was 26.73 ± 23.55 months. The difference between the results of the CHOP-INTEND test performed one day before the 4 doses was analyzed by the Friedman test, which was used to compare more than 2 measurements in dependent groups. There was a statistically significant difference between the four evaluations (χ2: 14.356, p = 0.002). The Wilcoxon Signed Ranks test was performed on the 2 groups to determine from which measures the difference was origined. Accordingly, there were significant differences between 1-4, 2-4, and 3-4 CHOP-INTEND evaluations. The results of the study showed that 21 babies were developing as clinically and/or statistically. It was observed that infants with better initial functional level were more likely to benefit, and that the progress of the treatment period was associated with an increased use of this benefit. No serious side effects were observed during the follow-up period. These results suggest that Nusinersen may be an appropriate treatment option for early onset SMA disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.197

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Interim report on the safety and efficacy of longer-term treatment with nusinersen in infantile-onset spinal muscular atrophy: results from the SHINE study

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Nusinersen has demonstrated a favorable benefit:risk profile and shown significant and clinically meaningful efficacy on motor function across a broad spectrum of SMA populations, and event-free survival (EFS; time to death or permanent ventilation) in infantile-onset SMA. The current analyses report interim results from the SHINE study (NCT02594124) for individuals with infantile-onset SMA who transitioned from ENDEAR. SHINE is an open-label extension study for infants/children who participated in the nusinersen clinical trial program. Nusinersen doses were administered according to participant's previous trial cohort/regimen. The primary endpoint is safety/tolerability; secondary endpoints include achievement of HINE-2 motor milestones and EFS. The cutoff date was June 30, 2017; 89 infants transitioned from ENDEAR, 65/81 were previously randomized to nusinersen and 24/41 to sham-control. Within SHINE only, 83 infants had an adverse event (AE); most frequent AEs were pyrexia and upper respiratory tract infection; no treatment-related serious AEs. Mean (95%CI) change in HINE-2 total score from nusinersen initiation to last observed visit was 1.1 (0.20-1.90) for infants who received sham-control in ENDEAR and nusinersen in SHINE (n=20/24) and 5.8 (4.58-7.04) for those who received nusinersen in ENDEAR and SHINE (n=74/81; pooled ENDEAR/SHINE data). Median (95%CI) EFS time among sham-control infants in ENDEAR was 22.6 (13.6-31.3) weeks vs 73.0 (36.3-NA) weeks for those who received nusinersen in ENDEAR and SHINE. For infants who received nusinersen in ENDEAR and SHINE, 23/81 (28%) achieved full head control and 12/81 (15%) independent sitting as their highest motor milestone; no infants had yet achieved standing unaided/walking independently, although some made gains in precursors to both. Motor function and EFS improved in infants who initiated nusinersen in ENDEAR and motor function stabi-

lized or started to show improvement in those who initiated nusinersen in SHINE.

http://dx.doi.org/10.1016/j.nmd.2018.06.198

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Transforaminal intrathecal delivery of nusinersen using cone-beam computed tomography in children with spinal muscular atrophy: results of technical success and safety

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Nusinersen, the only treatment approved by the United States Food and Drug Administration for spinal muscular atrophy (SMA), is delivered intrathecally. Many children have a history of severe scoliosis and/or spinal fusion with instrumentation making access to the thecal space challenging using the standard interlaminar approach. The use of fluoroscopic guidance is complicated by the rotoscoliosis that is frequently found in children with SMA. Computed tomography (CT) facilitates cervical, caudal, and transforaminal approaches to the thecal space when the more traditional approach is not possible. This study, from one tertiary care pediatric hospital, describes the experience using cone-beam CT guidance with two-axis fluoroscopic navigational overlay to deliver intrathecal nusinersen in children with SMA who have spinal hardware precluding the standard posterior lumbar puncture technique. Results include a description of the technical success, complications and radiation dose over an 11-month period. We conducted a retrospective review of 36 consecutive nusinersen injections performed in 8 children with SMA who have extensive spinal hardware precluding the standard posterior lumbar puncture technique. An interventional radiologist, using a transforaminal thecal approach, employed cone-beam CT with navigational overlay to deliver nusinersen. We analyzed results including technical success, complications and total fluoroscopy time. Results: All transforaminal injections were technically successful. There were no major complications that occurred. We report 3 minor complication including; 2 complaints of transient radicular pain which resolved immediately after the spinal needle was removed and one post-procedural neuropathic headache that was attributed to positioning required for the procedure. This latter complication resulted in an overnight hospital stay and resolved after a short-term treatment with gabapentin. Radiation dosing was reported in 35 of 36 injections as data was not available for one injection. The average procedural fluoroscopy time and air kerma were 1.23 min and 73.54 mGy, respectively. Cone-beam CT guidance with two-axis navigational overlay is a safe, effective method for gaining transforaminal intrathecal access in children with spinal abnormalities and hardware precluding the use of standard techniques.

http://dx.doi.org/10.1016/j.nmd.2018.06.199

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Retrospective study in children with SMA treated by intrathecal Nusinersen

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To describe the experience of treatment by intrathecal Nusinersen in children with SMA, focusing in the tolerance, technical strategies and functional results. A retrospective study was performed at Garches Hospital in the first 30 SMA patients treated by intrathecal Nusinersen. The standard schedule was followed (day 1, 14, 28, 60 and every 4 months thereafter) and a multidisciplinary assessment was performed before treatment and prior to injections 5 and 6. It included clinical, cardio-respiratory (ECG, FVC), radiological (EOS, osteodensitometry), urinary and blood tests (renal function, hemostasis), and motor function scales (CHOP intend, HINE, MFM). Genetic, clinical and complementary data were reviewed. All 30 patients were treated by lumbar puncture (115 procedures). Mean age was 9.3 years (1-19 y). SMA type distribution was: type 1 with 2 copies *SMN2* (1 patient; age 4m), type 1c with 3 *SMN2* (5 patients; 3-16y), type 2 (21 patients; 4-19y), type 3 (3 patients; 7-15y). Mechanical ventilation was required in 18 patients before onset (16 nocturnal noninvasive; 2 tracheostomy). Seven patients had previous spinal surgery (4 growing rods; 3 arthrodesis) and were injected guided by CT-scan or radioscopy. Besides, lumbar ponction in three children with severe scoliosis was possible guided by portable X-rays. Most treatments were performed in the daily hospital facility. No severe adverse events were observed and common side effects recorded were mostly attributed to post injection syndrome. All patients are currently alive. No loss of acquisition was observed and new abilities in motor function were reported in 12 patients (40%). The SMA 1 child treated at 4 months acquired sitting at 10m, he has normal growth parameters and he does not require enteral nutrition nor ventilatory support at 21 months. Analysis of serial motor and functional tests at 6 and 12 m is undergoing. Preliminary short-term results using intrathecal Nusinersen showed good tolerance and no motor impairment in the patients. Clear response was observed in an early treated type 1 child. In later forms, several patients improved from the first four injections. No major changes were observed in half of the patients but sensibility to change in the tests used may need longer follow-up to compare with course in untreated children when available

http://dx.doi.org/10.1016/j.nmd.2018.06.200

P.173

Spinraza experience in Dallas

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Spinal muscular atrophy (SMA) is a disease of motor neurons that affects mostly infants and children and is caused by mutations in the *SMN1* gene. Spinraza was approved by the FDA on December 23, 2016, for treatment of SMA. We first began giving Spinraza via the Expanded Access Program (EAP) provided by Biogen for type I patients in December, 2016. We organized a program for SMA patients beginning with diagnosis, proceeding through preauthorization and scheduling. We report our results after 17 months of treating patients commercially. This was a retrospective chart review of all SMA patients treated with Spinraza. Data was collected from the electronic health record (EHR). As of April, 2018, 47 children received at least one dose of Spinraza. Sixteen were type I, aged 2 months to 11 years, 16 were type II, aged 2 to 17 years, and 11 were type III, aged 4 to 12 years. Five patients were initially on the EAP. One type II and 14 type I patients were beyond the age range included in the clinical trials at the time of first injection. Three children received drug via lumbar Ommaya ports and one received injection via cervical intrathecal space. Nine required fluoroscopic imaging. At least 2 patients required CT scans of the whole spine to determine feasibility for access to the intrathecal space. Patients past infancy required some type of anesthesia. Motor outcome measures appropriate for age and function (CHOP INTEND, HFMS, and PUL) were obtained at baseline and follow up. Adverse effects of drug or procedure were few. It is feasible to deliver Spinraza to a large and diverse population of children with SMA. It is too early to determine if our commercial patients benefit from drug as well as subjects enrolled in research protocols.

http://dx.doi.org/10.1016/j.nmd.2018.06.201

P.174

Lumbar catheter placement for nusinersen administration in a SMA 2 patient with spinal deformities and previous spinal surgery

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Spiranza (nusinersen) is the only treatment currently available for spinal muscular atrophy (SMA) and is delivered intrathecally. In children and adults with long disease duration is usual the presence of spinal deformities and previous spinal surgery that precludes the use of standard techniques of lumbar puncture. In clinical practice, it is becoming even more frequent the need of new ways of accessing the intrathecal space, especially when a repetitive administration route is needed. To present the complications and benefits of lumbar catheter placement for Spiranza administration in a patient with previous spinal surgery. A 22-year-old female, with long standing diagnosis of SMA type 2 confirmed by genetic testing, and with 3 *SMN2* copies, underwent the lumbar puncture for the administration of the first and second doses of Spiranza, that was very difficult and painful. She had a past spinal surgery when she was 8 years old. Thus, we decided to place a lumbar catheter using open surgery under general anesthesia. No complications after the procedure occurred. The patient referred only local pain related to surgical procedure and since then the administration of Spiranza has been performed through the lumbar catheter. Placement of a permanent lumbar catheter is an option to be considered in patients with SMA who present with great difficulty for repeated intrathecal administration of the Spiranza.

http://dx.doi.org/10.1016/j.nmd.2018.06.202

P.175

Intrathecal nusinersen in spinal muscular atrophy: case series in Argentina

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Nusinersen is the only treatment available, as a disease modifier, for spinal muscular atrophy (SMA). Its use and experience is limited in Argentina to know under the regime of compassionate use. To evaluate response to intrathecal nusinersen in a group of patients. Nusinersen was started in 11 patients. Of these, 7 completed induction (range 2-18 year old, 5 boys, one with SMA 1, six with SMA and reached an evaluation point of 6 months from the start of treatment. In this group, WHO milestones, Hammersmith, ULM, respiratory parameters, tolerance to treatments were evaluated. In 4 patients improvement was observed in Hammersmith scales, 6 patients improved in ULM and 4 patients acquisition in WHO Milestones. Overall, 6 of the 7 patients experienced at least one improvement in the evaluation of the motor. The patient with AME 1 did not show changes in motor patterns, but the speed in the NIV requirement. Adverse effects, 4 cases post-puncture syndromes (total 28 punctures), 2 atelectasis (same patient), 1 proteinuria, 1 fever. Although the treatment time is limited, at 6 months, 6 of 7 patients, the improvement in at least one of the motor scales evaluated.

http://dx.doi.org/10.1016/j.nmd.2018.06.203

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Experience using Spinraza to treat adults with spinal muscular atrophy

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Evaluate effectiveness of spinraza clinical protocol in adults with SMA and determine post-treatment functional changes. Natural history data of functional and clinical measures prospectively collected from adults in a SMA network, PNCRN, were compared with spinraza treated adults. Visits included medical & genetic history, establishing standards of care, evaluating anatomic and radiologic findings, and assessing insurance. A minimal data set included at least one of the following: modified CHOP-INTEND, RULM, HFMSE, TUG, 6MWT. We also monitored pulmonary function, limb strength, patient reports, safety labs and adverse events. Natural history was collected from 170 evaluations of 57 untreated adults. Assessments included 39 patients wanting spinraza, 27 treated. None were denied treatment due to insurance, but others have not yet received treatment due to lack of access via fluoroscopy (n=5), and patient choice (n=1). Treated individuals were: 18-65 years old, non-ambulatory (n=20), male (n=16), requiring day and night ventilatory support (n=7), and spinal fusion (n=8). Attestations of qualitative improvements were frequent (85%) but were not reflected in the spinal muscular atrophy functional rating scale (SMAFRS). Baseline measures (median and ranges) included for ambulatory (n=7): 6MWT (342.7m, 69.2-466.0m), TUG (9.9s, 8.4-44.2s) and for non-Ambulatory RULM (n=14) (6, 0-37), FVC (n=12) (1.6L, 0.28-3.8L);(%predicted 40%, 9-90%)). Spinraza has been well tolerated and improvement trends are emerging in multiple measures; data continue to be collected. Analyses of clinical outcomes, to be presented, will define Spinraza efficacy for adults with SMA.

http://dx.doi.org/10.1016/j.nmd.2018.06.204

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AVXS-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1: event-free survival and achievement of developmental milestones

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Children with SMA1 are unable to sit unassisted, almost none achieve a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥40 by 6 months, and 92% die or require permanent ventilation by 20 months. The AVXS-101 trial explores safety and efficacy of a one-time intravenous administration of survival of motor neuron gene replacement therapy in SMA1. In this phase 1 trial, SMA1 patients received AVXS-101 at low dose (cohort 1, n=3) or proposed therapeutic dose (cohort 2, n=12). The primary objective was safety; secondary objectives included survival (avoidance of death/permanent ventilation) and ability to sit unassisted. CHOP-INTEND scores and other motor milestones were recorded. As of August 7, 2017, all patients were alive and event-free at 20 months of age and did not require permanent ventilation. Cohort 2 patients demonstrated improved motor function: 11/12 had CHOP-INTEND scores ≥40 points; 11/12 were able to sit unassisted for ≥5s, 10 for ≥10s, and 9 for ≥30s; 11/12 achieved head control and 9 could roll over. Two patients were able to crawl, pull to stand, stand, and walk independently. Asymptomatic transient rise in serum aminotransferase levels occurred in 4 patients and were attenuated by prednisolone. In contrast with natural history, AVXS-101 appeared to improve survival of both cohorts and motor function of cohort 2; 11/12 patients achieved CHOP-INTEND scores and motor milestones rarely or never seen in this population. No waning of effect or regression in motor function was reported; a 24-month update will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.205

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AVXS-101 phase 1 gene therapy clinical trial in spinal muscular atrophy type 1: improvement in respiratory and bulbar function reduces frequency and duration of hospitalizations compared to natural history

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We report data on requirements for nutritional and ventilatory support, and hospitalizations in SMA1 patients treated with AVXS-101, a gene replacement therapy. Twelve patients with SMA1 received a one-time, intravenous, proposed therapeutic dose of AVXS-101 (NCT02122952). At baseline, 7/12 patients did not require nutritional support, and 10/12 did not require ventilatory support. As of August 7, 2017, 6/7 patients who did not require nutritional support pre-dosing continued to eat exclusively by mouth, 11/12 could eat orally, and 7/10 who did not require ventilatory support pre-dosing continued without ventilatory support. Ten patients were hospitalized for respiratory infections, but all survived without need for tracheostomy or permanent ventilation. Patients treated with AVXS-101 spent a smaller percentage of time hospitalized (median of 2% [range=0-18.3]) in contrast with untreated SMA1 patients in the ENDEAR study (13.9% [0-75]). Ten of 12 patients treated with AVXS-101 were hospitalized <10% of the time (in contrast with 11/27 untreated patients, ENDEAR), and none were hospitalized ≥20% of the time (10/27 untreated patients, ENDEAR). The mean unadjusted annualized hospitalization rate (hospitalizations/number of subject-years followed) for patients treated with AVXS-101 was 2.0 (standard deviation=2.26), which was half that in the ENDEAR control group (4.3). The mean hospital stay was 7.1 days (range=3-12.1) in patients treated with AVXS-101, compared with 13 days reported in untreated patients. In contrast to natural history, SMA1 patients treated with AVXS-101 showed a reduced need for nutritional and ventilatory support, and reduced frequency and duration of hospitalizations.

http://dx.doi.org/10.1016/j.nmd.2018.06.206

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AVXS-101 trial experience: CHOP-INTEND effectively quantifies early, rapid, and sustained improvements that precede subsequent milestone achievement but is not sensitive to continued advances in motor function in infants with SMA type 1

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The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) quantifies the natural decline of motor skills in spinal muscular atrophy type 1 (SMA1) infants (maximum score=64). By 6 months of age, SMA1 infants almost never achieve a CHOP-INTEND score ≥40 points. We aimed to assess the sensitivity of the CHOP-INTEND to improvement in motor skills of infants treated with AVXS-101 gene replacement therapy. Twelve SMA1 infants (median age=3.1 months) who received a one-time, intravenous, proposed therapeutic dose of AVXS-101 (NCT02122952) underwent CHOP-INTEND assessments monthly (subsequently changed to quarterly in year 2) over a 24-month follow-up interval. Rapid response in CHOP-INTEND was observed with mean increases of 9.8 points at 1 month and 15.4 points at 3 months post-dosing; 11/12 patients achieved a score of ≥40 at a mean age of 5.3 months. Eleven of 12 sat unassisted and rolled without a commensurate change in score (August 7, 2017). Discordant with achievement of sitting unassisted at a mean of 15.9 months post-dose, the mean CHOP-INTEND score plateaued at 54 at approximately 9.9 months post-dose in the 9 children who sat unassisted for ≥5 seconds, but did not achieve the scale maximum. CHOP-INTEND identifies an early rapid treatment response in AVXS-101-treated infants, demonstrating departure from natural history. However, the CHOP-INTEND ceiling limits its sensitivity to predicting motor milestone achievement. To accurately detect further gains in motor function beyond that historically achieved by SMA1 children, additional assessment tool(s) with advanced items are necessary (eg, Bayley-III).

http://dx.doi.org/10.1016/j.nmd.2018.06.207

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AVXS-101 phase 1 gene replacement therapy clinical trial in spinal muscular atrophy type 1: patients treated early with the proposed therapeutic dose were able to sit unassisted at a younger age

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SMA1 is a devastating monogenic neurodegenerative disease. Children with SMA1 are unable to sit unassisted, and by 6 months, almost none achieve a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score ≥40 points (maximum 64). This study explored whether motor milestone achievement in SMA1 patients treated with a one-time dose of AVXS-101 gene replacement therapy was related to age at dosing. Twelve patients received an intravenous, proposed therapeutic dose of AVXS-101 (NCT02122952). CHOP-INTEND scores and motor milestones were evaluated. CHOP-INTEND assessments occurred monthly (subsequently changed to quarterly in year 2) over a 24-month follow-up interval. As of August 7, 2017, 11/12 patients achieved and maintained CHOP-INTEND scores ≥40, and 10/12 achieved and maintained scores ≥50; both significantly differ from the published natural history (Exact Binomial test; $P<0.0001$). Eleven of 12 patients achieved the ability to sit unassisted for 5 seconds or longer; 9/12 achieved the ability to sit unassisted for 30 seconds or longer. Patients who received the AVXS-101 dose at ≤3 months of age reached the 5-second milestone at a younger age (median 12.5 months, n=6) than those dosed >3 months of age (median 21.6 months, n=5) (Wilcoxon non-parametric 2-sample test, $P=0.0087$). Eleven of 12 patients achieved levels of motor function not seen in SMA1 patients. The majority of patients achieved sitting unassisted, regardless of age at dosing, however, those dosed early achieved this milestone more quickly, emphasizing the need for newborn screening for SMA. An update will be given at presentation.

http://dx.doi.org/10.1016/j.nmd.2018.06.208

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AVXS-101 gene replacement therapy for spinal muscular atrophy type 1: pivotal study (STR1VE) update

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In the phase 1 study (NCT02122952), AVXS-101, a potential SMN gene replacement therapy, improved survival and motor function in SMA1 patients. In contrast with natural history, increased motor function, measured by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), was detected as early as 1 month, and increased to levels that are not observed in the natural history of SMA1. Four patients experienced asymptomatic transient elevations in serum aminotransferase soon after dosing and were attenuated by prednisolone. We report study design and baseline demographics of STR1VE, a phase 3 study (NCT03306277) investigating efficacy and safety of AVXS-101. STR1VE is a multicenter (16 sites), open-label, single-arm, one-time-dose study in a minimum of 15 SMA1 patients <6 months of age (bi-allelic SMN1 mutations, 1-2xSMN2).

For the first 3 patients, a 4-week dosing interval allowed review of safety and early signs of efficacy prior to dosing the next patient. Primary outcomes are independent sitting for 30 seconds at 18 months of age, and survival (avoidance of death/permanent ventilation) at 14 months. As of January 30, 2018, 3 SMA1 patients (2xSMN2) have been enrolled. Age at enrollment and symptom onset was 2.7 months (1.8-4.3 months) and 1.0 months (0.5-2.0 months). The mean baseline CHOP-INTEND score was 24.3 (18-34). No patients required ventilatory or nutritional support. The AVXS-101 phase 3 study investigates efficacy and safety of a one-time intravenous infusion of AVXS-101 in SMA1 patients. Updated patient data with follow-up will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.209

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Early diagnosis and speed to effect in infant-onset spinal muscular atrophy

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SMA type 1 (SMA1) is marked by a rapid, precipitous loss of motor neurons; thus, it is critical that a disease modifying therapy achieves an immediate pharmacological effect to arrest further motor neuron loss. In the pivotal nusinersen phase 3 study (ENDEAR), ~10% of subjects died or required permanent ventilation by 2 months, the time required to complete four loading doses over the initial 2-month loading dose interval, and almost one-third of subjects died or required permanent ventilation by 6 months from dosing. This may reflect a non-immediate therapeutic effect. This study explored the rapidity of AVXS-101 therapeutic effect as measured by early changes in CHOP-INTEND compared with the response to nusinersen demonstrated in the ENDEAR study (≤5-point increase in CHOP-INTEND at 2 months post dosing). SMA1 patients were treated with AVXS-101 (NCT02122952; study cohort 2; N=12; up to 24 months). Motor function improvements with AVXS-101 were assessed using changes in the CHOP-INTEND score from baseline to months 1 and 3. All patients treated with AVXS-101 survived event-free to 24 months with a rapid increase in mean CHOP-INTEND of 9.8 points as early as 1 month and 15.4 points at 3 months post dose were observed. AVXS-101 appears to induce a more rapid improvement in motor function as measured by CHOP-INTEND score relative to nusinersen, which is consistent with its pharmacological mechanism of action that is designed to timely restore SMN expression in motor neurons with a single dose administration. Advances in the understanding of SMA, currently available and investigational pharmacologic treatments, and the gene replacement therapy, AVXS-101, underscore the importance of early diagnosis and treatments with a near-immediate onset of action to maximize clinical improvements.

http://dx.doi.org/10.1016/j.nmd.2018.06.210

MITOCHONDRIAL DISEASES (Posters)

P.183

MELAS and reversible cerebral vasoconstriction

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A 22-year-old woman was admitted due to fever and severe headache for 10 days and altered mental status and generalized tonic-clonic seizures for 8 days. She had a short stature and hairy body surface, and her mother passed away about ten years ago due to “encephalitis”. Laboratory data showed elevated lactate in both peripheral blood and CSF. Brain MRI using diffusion weighted imaging revealed hyperintense lesions located in the whole right temporal and occipital lobes and pulvinar of thalamus. MR angiography revealed segmental stenoses at the right P1 and M2-3 junction. Muscle biopsy showed typical RRF and SSV. A genetic study revealed a mitochondrial DNA A3243G point mutation. The patient’s clinical symptoms and MRI/MR angiography (MRA) findings improved after the administration of L-arginine, L-carnitine, lipoic acid, vitamin B and dexamethasone. Therefore we speculate the possible pathophysiology just like RCVS (reversible cerebaral vasoconstriction syndrome) involving in the stroke-like episodes of MELAS.

http://dx.doi.org/10.1016/j.nmd.2018.06.211

P.184

Hypercapnic respiratory failure is common presentation in A3243G-related mitochondrial myopathy

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The A3243G mutation in the mt-tRNA(Leu) gene, first described in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke like episodes (MELAS), accounts for approximately 80% of mutations in individuals with MELAS syndrome. Although originally described in families with a classical syndrome of MELAS in muscle biopsy, the A3243G mutation is increasingly recognized to exhibit marked phenotypic heterogeneity. This paper describes the clinical, laboratory and histopathology features of an unusual phenotype in 3 family harboring the A3243G ’MELAS’ mutation. We present all the cases with middle-aged, who developed mid-life respiratory failure necessitating non-invasive ventilator support. Brain MRI excluded the lesions of the central nerve system. Mitochondrial histochemical abnormalities included ragged-red fibers and excessive COX-deficient fibers and mtDNA sequencing identified the A3243G mutation commonly associated with the MELAS phenotype. This case extends the evolving phenotypic spectrum of the A3243G mutation and emphasizes that it may cause isolated mitochondrial myopathy with respiratory failure, with marked histochemical defects in muscle. Our findings support consideration of screening of this gene in cases of isolated mitochondrial myopathy with respiratory insufficiency.

http://dx.doi.org/10.1016/j.nmd.2018.06.212

P.185

***MTTL* 3243A>G mutation in a patient with a pure mitochondrial myopathy mimicking a distal myopathy, a striking uncommon phenotype**

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Mutations in transfer RNAs (tRNAs) constitute “hotspots” for mitochondrial disorders, particularly *MTTL* 3243A>G with MELAS (myopathy, encephalopathy, lactic acidosis, stroke like episodes). Rarely, it may manifest as a pure limb-girdle myopathic form. We present a patient with a pure myopathic form, mimicking a distal myopathy. The aim is to describe a patient with an unusual phenotype associated with the *MTTL* 3243A>G mutation. Case report. 44 y-o female with normal development, no muscle complaints until age 40 when she begins with difficulty climbing stairs and mainly walking on tiptoes or on heels. No sensory symptoms, “stroke like” events, hearing loss, migraine or visual difficulties. Two healthy children, maternal grandmother with unspecified cardiac disorder, with no muscle weakness. Deceased mother with muscle weakness treated as an inflammatory myopathy without response. On physical examination, no obvious palpebral ptosis or ophthalmoparesis. She was unable to walk on tiptoes or on heels, with asymmetric calf hypotrophy. She has proximal muscle weakness 4/5 in upper and lower limbs, 4-/5 tibialis anterior and gastrocnemius. Normal spirometry, echocardiogram and brain MRI. Quadriceps muscle biopsy: Oxidative defects with ragged red and COX negative fibers. mtDNA sequencing (muscle tissue): *MTTL* 3243A> G with 85% heteroplasmy. Muscle imaging of the lower limbs showed severe bilateral involvement of tibialis anterior and gastrocnemius medialis, and to a lesser extent of the lower leg muscles. At thigh level, the sartorius was selectively involved with relative sparing of the

semitendinosus. *MTTL* 3243A>G mutation is present in 80% of patients with the clinical spectrum of MELAS. To the best of our knowledge, pure myopathic forms with predominantly distal involvement with this mutation have not previously been reported. In addition to *POLG* mutations, *MTTL* should be considered in mitochondrial myopathies with mainly distal involvement.

http://dx.doi.org/10.1016/j.nmd.2018.06.213

P.186

Muscle histopathology in infantile *DNM1L*-related mitochondrial epileptic encephalopathy is key for clinical diagnosis

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We describe 5 sporadic patients affected by severe mitochondrial treatment-resistant seizures correlated with *de novo* heterozygous mutations in *DNML1*. The most consistent finding in all patients was a histopathological peculiar pattern. Molecular genetic analysis disclosed heterozygous *de novo DNML1* mutations in 5 patients, and 3 of these mutations were novel. Unreported mutations were validated in a yeast model.Summarizing the clinical reports of the 5 patients, in all first symptoms appeared between the second and fifth year of life after normal developmental milestones occurring in the first year of life. The first manifestation consisted in prolonged treatment resistant.generalized clonic seizures or hemiclonic seizures that shortly progressed into frequently recurrent epileptic mal status. The brain MRI showed at the beginning T2 hyperintensities in the posterior white matter regions and transient T2 hyperintensities in the cortical areas in 2 patients when performed serially. With time, the MRI showed moderate to severe global cerebral atrophy in all patients Histopathology of the muscle biopsy was revised in 4 patients and showed peculiar features: scattered fibers with a partial reduction of cytochrome c oxidase (COX) and succinate dehydrogenase (SDH) stain with aspects of polymorphic core like areas. These areas corresponded to reduced immunoreactive areas displayed by immunohistochemistry with antibodies recognizing TOMM20, defining abnormally distributed mitochondria. Biochemical spectrophotometric assay of the mitochondrial OXPHOS enzymes showed normal activities. In culture fibroblasts we observed an increased filamentous network in mutant fibroblasts in 3 patients, while in one patient the mitochondrial network appeared as normal controls and in the last patient we observed a "chain-like" structure, not observed in controls but already reported in patients with mutations in *DNM1L*.

http://dx.doi.org/10.1016/j.nmd.2018.06.214

P.187

Mitochondrial disorders with polymerase gamma 1 (*POLG1*) mutations: a study from tertiary referral centre

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Mitochondrial disorders are a heterogeneous and a complex group of neuromuscular disorders resulting from dysfunction of oxidative phosphorylation (OXPHOS). Defects in enzymes encoded by nuclear genes (nDNA) or mitochondrial genome (mtDNA) cause myopathy. The nuclear genome encodes most of the subunits of enzyme complexes, assembly proteins and mtDNA replication, transcription and translation, while, the mitochondrial genome encodes 13subunits of the OXPHOS system, rRNA and tRNA. The cross talk between nDNA and mtDNA is crucial for the cellular regulation of mtDNA integrity, copy number and mitochondrial protein production. POLG1, a nuclear gene essential for mtDNA replication encodes for the catalytic subunit of mitochondrial polymerase gamma. Mutations in POLG1 results in a spectrum of clinical phenotypes. In this study, 910 patients seen between 2002-2017, clinically fulfilling the modified Walkers criteria who underwent skeletal muscle biopsy were analyzed. Long range PCR done on 630/910 cases, revealed multiple deletions in 71. We have sequenced intron-exon boundaries of *POLG1* in 351 cases (71 cases with multiple deletions and 280 cases where deletions could not done). Mutations were identified in 18/351(5%) patients. The most common clinical phenotype noted in these 18 cases was CPEO. There were 9 males and 9 females with age at onset ranging from 2 -20 years. Morphologically, muscle biopsy revealed characteristic ragged red fibres with ultrastructural evidence of abnormal mitochondria in 8 cases. Respiratory chain analysis revealed a multiple complex deficiency in 8/18. The reported mutations identified include p.L304R (n=10), p.A682T(n=1), p.R1097G (n=1), p.E1143G (n=1), p.H110Y & p.E1143G (n=1), p.R1187W (n=1), p.R627Q (n=1). In addition, two novel mutations p.Q49H and p.V1106A were noted. In our cohort, a p.L304R mutation was more prevalent and seen in younger age group. Detailed clinical, biochemical, pathological and genetics findings will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.215

P.188

Novel *POLG* mutations and variable clinical phenotypes in 5 Chinese patients with mitochondrial diseases

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POLG related mitochondrial disorders has rarely been reported in China. Here we report 5 unrelated Chinese patients (2 males and 3 females) with mitochondrial disease caused by *POLG* gene mutations. Two of them had a dominant family history and 3 were sporadic cases. The ages of onset were from 15 to 40 years old, with disease course ranging from 1 to 26 years. Clinically, 1 case were conformed with SANDO (sensory ataxic neuropathy, dysarthria and ophthalmoparesis) syndrome, 2 cases with autosomal dominant progressive external ophthalmoplegia (PEO), 1 case with autosomal recessive PEO, and 1 case with sensory axonal neuropathy and mental retardation. Laboratory examination revealed normal or mild elevation of serum creatine kinase level. Electromyography revealed myopathic or neurogenic pattern. Nerve conduction studies showed decreased amplitude of nerve action potential in 3 cases, with sensory nerve predominantly involved. Mitochondrial abnormality appeared in 4 patients who underwent muscle biopsies. Sural nerve biopsy revealed chronic axonal neuropathy in the patient with sensory axonal neuropathy and mental retardation. Genetic test revealed compound heterozygous POLG mutations in 3 sporadic patients and single heterozygous mutations in 2 dominant inherited patients. c.914G>A (p.S305N), c.924G>T (p.Q308H), c.1613A>T (p.E538V), c.1612G>T (p.E538*), c.1790 G>A (p.R597Q) and c.3002delG. were novel mutations. Novel mutations found in this study expanded the mutational spectrum of *POLG*.

http://dx.doi.org/10.1016/j.nmd.2018.06.216

P.189

A novel case of *MSTO1* gene related congenital muscular dystrophy with cerebellar involvement

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Recessive mutations in the *MSTO1* gene, encoding for a mitochondrial distribution and morphology regulator, have been recently described in 4 families with multisystem involvement, mostly characterized by myopathy or dystrophy, cerebellar ataxia, pigmentary retinopathy and raised CK. Here we report a patient with recessive *MSTO1* gene related muscular dystrophy and ataxia. The patient, born to non-consanguineous parents, presented at age 2 years with global developmental delay. At age 15 years he was ambulant and showed axial, upper and lower limb weakness, pronounced proximally,

scoliosis, ankle contractures and ataxia. There was no cardiac or respiratory involvement. EMG was normal. Brain MRI at 6 years showed cerebellar atrophy and mild under-opercularisation of the left Sylvian fissure; when repeated at 9 years, there was mild progression of cerebellar atrophy and additional supratentorial sulcal prominence suggestive of volume loss. Muscle MRI showed generalized increase in T1 signal in the lower limb with normal STIR sequences. CK was raised (800-1614 IU/L). Muscle biopsy showed fibre size variability, increased internal nuclei, fatty endomysial infiltration, few regenerating fibres, type 1 predominance and some minicores. Minor changes of uncertain significance on laminin-α and a-dystroglycan staining were observed. Respiratory chain enzyme studies were normal. Whole-exome sequencing revealed 2 missense MSTO1 variants. The first variant (c.766C>T p.(Arg256Trp)), affecting a conserved residue in the tubulin domain of the protein, is reported in the gnomAD dataset with an allelic frequency of 0.00003, while the second (c.1435C>T p. (Pro479Ser)) is novel. In silico tools predict both variants as damaging. Phasing of the variants is in progress. This case confirms a consistent phenotype associated with recessive *MSTO1* gene mutations and suggests that progressive cerebellar atrophy can be a feature of the condition.

http://dx.doi.org/10.1016/j.nmd.2018.06.217

P.190

Novel variant of *GOSR2* gene in a patient presenting with mitochondrial myopathy and epilepsy

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GOSR2 gene is a Golgi vesicle transport gene which encodes for the Golgi SNAP receptor complex member 2 protein. This protein mediates transport between the medial and trans Golgi compartments. Homozygous mutations in *GOSR2* gene (variant c.403G>T, p.G144W) have been associated with progressive myoclonic epilepsy. Patients reported had mildly elevated creatine kinase but normal muscle biopsy and no symptoms of myopathy. One reported case with compound heterozygous *GOSR2* mutations (previously described mutation c.430G>T and a novel splice site mutation c.336+1G>A) presented with congenital muscular dystrophy. Here we report a case of congenital hypotonia and epilepsy with muscle biopsy findings consistent with mitochondrial myopathy. Patient was found to have compound heterozygous *GOSR2* mutations (paternally inherited previously described pathogenic mutation c.430G>T and a maternally inherited novel mutation c.22dup that was classified as likely pathogenic. We hypothesize that the novel variant of *GOSR2* gene found in this patient could be contributing to both pathologies (mitochondrial myopathy and epilepsy) together. Additionally, we hypothesize that *GOSR2* gene may be involved in mitochondrial structure formation and may play a role in the development of mitochondrial myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.218

P.191

Single muscle fiber analysis of extraocular and skeletal muscles in a CPEO patient harboring a pathogenic point mutation in the *MT-TN* gene

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Chronic progressive external ophthalmoplegia (CPEO) is a frequent feature of mitochondrial disorders and usually associated with mitochondrial DNA (mtDNA) mutations. Skeletal muscle (SKM) tissue is most frequently used for biochemical analyses and mitochondrial genome testing. However, extraocular muscle (EOM) is the clinically most affected tissue but usually not available for routine work-up. Consequently, systematic data on EOM is limited and the reason for preferential clinical affection remains unclear. We addressed this unsolved question by histochemical and genetic analyses of EOM and SKM single muscle fibers in a patient with isolated CPEO caused by a heteroplasmic point mutation in the *MT-TN* gene. The histochemical analysis showed higher absolute numbers of cytochrome c oxidase (COX)-deficient EOM fibers compared to COX-deficient SKM fibers. However, genetic analyses by restriction fragment length polymorphism revealed no significant difference in the mutation loads between COX-negative single muscle fibers in EOM compared to SKM. Quantitative single fiber real-time PCR revealed higher mtDNA copy numbers in single muscle fibers of EOM compared to SKM. COX-negative single muscle fibers of EOM and SKM showed significantly higher mtDNA copy numbers compared to COX-positive fibers suggestive of a compensatory mtDNA proliferation. We show that high loads of the *MT-TN* mutation correlate with a biochemical loss of COX activity in single muscle fibers of EOM and SKM at a similar threshold. The higher absolute numbers of COX-negative fibers in EOM compared to SKM might be caused by facilitated segregation of the mutation into the EOM providing thereby a possible explanation of the preferential ocular manifestation in CPEO.

http://dx.doi.org/10.1016/j.nmd.2018.06.219

P.192

Severe isolated mitochondrial myopathy in childhood

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Mitochondrial disorders often present as multisystemic diseases, but some patients only show symptoms in a single organ or tissue. Isolated myopathy as solitary manifestation of mitochondrial disease is relatively rare. They can present with myalgia, exercise intolerance, proximal muscle weakness or external ophthalmoplegia. The clinical course is variable; from rapidly progressive to static. Here we describe three pediatric patients with severe mitochondrial myopathy. The three male patients were from non-related parents. They presented at the mean age of 2.5 years with rapidly progressive myopathy characterized by proximal muscle weakness, shoulder girdle atrophy, and profound weakness of neck muscles with dropped head. They developed severe muscular hypotonia and two lost the ability to sit and walk. Non-neurologic manifestations were: respiratory insufficiency (2/3), apneas (1/3) and poor weight gain (3/3). Cardiac evaluation was normal (3/3). CK and lactic acid levels were increased in all. Brain MRI was unremarkable (3/3); MRS showed lactate peak (1/3). Treatment with coenzyme Q10, carnitine, riboflavin and thiamine did not show any effect. Muscle biopsies revealed increased mitochondrial proliferation with ragged red (2/3) and COX deficient fibers (3/3). Respiratory chain activity in muscle (2/3), showed severe complex I reduction (case 1) and multiplex complex deficiency (case 2). Mitochondrial DNA content was severe reduced (case 2). Molecular studies identified: case1, a homoplasmic variant on *MT-TL1* gene m.A>G3302, case2, biallelic mutations on *TK2* gene c.547C>T, (p.Arg183Trp) and c.416C>T (p.Ala139Val), case 3, a heteroplasmic variant on *MT-TL1* m.A>G3243. Mitochondrial disorders should be considered in the differential diagnosis of early onset severe isolated myopathy. Since they can be related to mitochondrial or nuclear DNA mutations, molecular diagnosis is essential for prognosis and genetic counseling.

http://dx.doi.org/10.1016/j.nmd.2018.06.220

P.193

Unexpected genetic diagnosis of mitochondrial disease in three consanguineous Turkish families

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Mitochondrial diseases are a clinically heterogeneous group of disorders caused by dysfunction of the mitochondrial respiratory chain. Some mitochondrial disorders affect a single organ, while many involve multiple systems such as skeletal muscle, brain, heart and liver, leading to diagnostic difficulties. Here we present three patients who were originally suspected to have a primary disease of skeletal muscle, leukodystrophy and brain malformation. Patients were recruited from three paediatric neurology clinics in Turkey: Izmir, Malatya and Diyarbakir. Whole exome sequencing (WES) was performed using Illumina exome capture (38 Mb target). Data analysis was carried out on the RD-Connect Genome-Phenome Analysis Platform (https://platform.rd-connect.eu/). Standard filtering criteria with MAF<1% and high/moderate VEP were used, as well as a list consisting of >5,000 medically interpretable genes. We identified a homozygous frameshift variant (p.Glu41GlyfsTer10) in *NDUFA12* and a homozygous missense variant (p.Gln85His) in *NDUFS3*, both associated with Leigh syndrome due to mitochondrial complex I deficiency (OMIM# 256000). We also identifid a homozygous nonsense variant (p.His158ProfsTer8) in *TACO1* associated with mitochondrial complex IV deficiency (OMIM# 220110), the second patient to be described worldwide so far. All the variants were highly pathogenic and were absent in the control population, suggesting they were disease-causing. Critical clinical review and metabolic analysis confirmed the mitochondrial deficiency. Next generation sequencing has the advantage of allowing an unbiased genetic diagnosis. We described three cases that had been initially diagnosed as myopathy, brain malformation and leukodystrophy, and WES resulted in the diagnoses of mitochondrial disorders. Importantly, this will allow for appropriate clinical management of these patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.221

P.194

Deficiency of the iron-sulphur cluster assembly protein ISCU causes impaired biogenesis or stability of respiratory chain complex I, II and IV in muscle

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Iron–sulphur cluster containing proteins are essential for iron homeostasis and respiratory chain function, with ISCU being among the most conserved proteins in evolution. Deficiency of the mitochondrial isoform due to deleterious mutations in the ISCU gene is associated with mitochondrial myopathy and exercise intolerance known as hereditary myopathy with lactic acidosis (OMIM #255125). Biochemical investigations demonstrate a characteristic profound complex II (succinate dehydrogenase, SDH) deficiency in addition to complex I and complex IV (cytochrome c oxidase, COX) deficiency. Muscle histopathology is typically associated with SDH deficiency as well as regional COX deficiency. We analyzed the expression of complex I to V of the respiratory chain by immunohistochemical and western blot analyses using antibodies to subunits of the five different enzyme complexes in muscle tissue of patients with homozygous or compound heterozygous deleterious *ISCU* mutations. The monoclonal antibodies we used were from Abcam and directed to subunit NDUFB8 (complex I), SDHB (Complex II), UQCRC2 (complex III), MTCO1 (complex IV), ATPB (complex V) and VDAC1 (mitochondrial marker). There was a reduced expression of complex I, II and IV subunits as demonstrated by western blot analysis. Immunohistochemistry showed that the deficiency was restricted to the same regions as the enzyme histochemical deficiency. The results demonstrate that the peculiar regional respiratory chain enzyme deficiency seen in hereditary myopathy with lactic acidosis is associated with deficiency of protein subunits of the corresponding respiratory chain complexes. Lack of ISCU protein thus affects the biogenesis, assembly or stability of several of the respiratory chain complexes, which appears to be an important mechanism that explains the enzyme deficiency and clinical symptoms.

http://dx.doi.org/10.1016/j.nmd.2018.06.222

P.195

A novel multiplex chromogenic immunoassay for evaluating mitochondrial respiratory chain complex I and complex IV defects in diagnostic muscle biopsies

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The investigation of clinically suspected mitochondrial disease (mtD) includes performing a skeletal muscle biopsy for biochemical/histochemical assessment of mitochondrial respiratory chain (RC) defects. COX-SDH histochemistry detects RC-complex IV (CIV) defects, but RC-complex I (CI) defects cannot be detected histochemically. CI/CIV defects are common in mtD. Immunohistochemical evaluation of RC-complex defects relies on reduced amount of the assembled complex associated with catalytic deficiency, detectable with RC subunit-specific monoclonal antibodies. Our aim was to design a dual chromogenic immunoassay (DCI) for evaluating CI/CIV defects in diagnostic muscle biopsies. In the DCI optimised protocol, primary antibodies (Abcam), TOMM20 (mitochondrial mass), NDUFB8 (CI) and MTCO1 (CIV) were coincubated (TOMM20+CI and TOMM20+CIV), and then TOMM20 developed to yellow and the other marker to teal (Discovery/Ventana Systems) with colocalising antibodies visualising as green. Control sections stained as a mosaic dark green (type I fibres) and light green (type II fibres) pattern. Completely CI/CIV-deficient fibres stained yellow, and partly CI/CIV-deficient fibres stained yellow-green, and were easily detectable due to good visual colour contrast. The DCI and COX-SDH assays were performed in serial frozen sections. 23 biopsies were assessed: 15 with genetically confirmed mtD (mtDNA rearrangements/point mutations/depletion), 4 with high clinical/histological suspicion of mtD, and 4 unaffected controls. % COX and CI/CIV-deficient fibres were counted in two random fascicles, with high concordance amongst % COX-negative and CI/CIV-deficient fibres. The DCI detected more CI-deficient fibres in 7/19 cases and more CIV-deficient fibres in 5/19 cases compared to COX-negative fibres (average 6%). Most COX-negative fibres had dual CI+CIV defects with DCI. Segmental and partial CI/CIV defects were detectable. Equivocal COX-SDH stained fibres were often strongly CI/CIV-immunodeficient. In conclusion, our multiplex DCI reliably detects CI/CIV defects comparable in sensitivity to the COX-SDH histochemical assay, is easy to evaluate due to a good visual contrast between CI/CIV positive and negative fibres and can be easily co-opted to routine diagnostic work. Studies are underway to develop a quadruple chromogenic immunoassay for digital evaluation of CI/CIV defects.

http://dx.doi.org/10.1016/j.nmd.2018.06.223

MITOCHONDRIAL DISEASES I (Oral)

I.4

Skeletal muscle manifestations in mitochondrial disease

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Besides their critical role in bioenergetics, mitochondria additionally display complex dynamic behaviors within cells, including fusion, fission, directed transport and targeted destruction (mitophagy). The relevance of these processes to human disease has been intensively documented over the last several years. While oxidative phosphorylation defects are classically associated with muscular dysfunction, more recent work indicates that genetic defects in mitochondrial dynamics are also associated with myopathy in mice and humans. Indeed, the long, cylindrical geometry of skeletal myofibers places unique demands on the mitochondrial population and limits functional homogeneity along the length of the fiber. Our efforts to measure mitochondrial dynamics in intact skeletal muscle has provided insight into the role of organelle behavior in modulating disease. We find that heterogeneity in mitochondrial fusion rates is not only a defining characteristic between mus-

cle fiber types, but also serves to functionally compartmentalize organelles along the length of a myofiber. Higher fusion rates are biochemically linked to functional oxidative phosphorylation, and localized regulation of mitochondrial dynamics can therefore promote homogenization of healthy organelles, while limiting the spread of dysfunctional organelles. Through these mechanisms, we propose that organelle dynamics is an important factor mitigating the pathophysiology of human mitochondrial disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.224

I.5
Perturbed mitochondrial homeostasis in the pathogenesis of mitochondrial disorders

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Mitochondrial disorders come with an impressive variability of symptoms, organ involvement, and clinical course, which considerably impact the quality of life and quite often shorten the lifespan expectancy. The last 20 years have witnessed an exponential increase in understanding the genetic and biochemical mechanisms leading to disease. More recently, several homeostatic pathways, including the quality control and adaptive mechanisms controlling the bioenergetics proficiency and biogenesis of the mitochondrial network, have become a central issue to elucidate pathogenic mechanisms and develop rational therapies in mitochondrial disease. Indeed, new experimental approaches have recently been emerging, some of which have shown potential efficacy at the preclinical level: for instance, activators of mitochondrial biogenesis, modulators of autophagy and mTORC1 pathway, and regulators of mitochondrial dynamics and mitochondrial architecture. We and others have shown that activation of the PGC1a-dependent mitochondriogenic axis partially rescues the phenotype of COX-deficiency mouse models. Conversely, suppression of ROS production by expressing the alternative oxidase (AOX) worsens the phenotype and anticipates the fatal outcome of a mouse model of COX deficiency restricted to skeletal muscle (Cox15sm/sm). Autophagy is an intracellular recycling process that delivers misfolded proteins and dysfunctional organelles to lysosomes. This bulk degradation process may be impaired in several pathological conditions including mitochondrial disorders, where its activation can be exploited for the clearance of dysfunctional mitochondria and the restoration of the normal energy homeostasis and metabolism. Rapamycin is an inhibitor of mTOR complex 1 (mTORC1) that can both induce autophagy, through new autophagosome formation, and increase the autophagic flux by enhancing lysosomal biogenesis. Rapamycin improves the clinical conditions of the Cox15sm/sm mouse model, rescuing the myopathy caused by COX deficiency. This is the result of a coordinated activation of autophagy together with increased lysosomes, possibly through the action of TFEB, a master regulator of lysosomal biogenesis.

http://dx.doi.org/10.1016/j.nmd.2018.06.225

MITOCHONDRIAL DISEASES II (Oral)

I.6
Deoxynucleoside therapy for mitochondrial DNA depletion disorders

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Encoded by the nuclear DNA gene *TK2*, thymidine kinase 2 is a mitochondrial protein required for synthesis of pyrimidine deoxynucleoside triphosphate (dNTP) building blocks for mitochondrial DNA (mtDNA) replication. TK2 phosphorylates the nucleosides thymidine (dT) and deoxycytidine (dC) to generate thymidine monophosphate (dTMP) and deoxycytidine monophosphate (dCMP). Autosomal recessive mutations of TK2 cause depletion and multiple deletions of mtDNA that manifest predominantly as myopathy. This rare disease typically begins in childhood and progresses to fatality. We generated and characterized a *Tk2* H126N knockin mouse model of the human disease. We initially tested "molecular bypass therapy" with dCMP+dTMP in the *Tk2* knockin mice. The treatment ameliorates biochemical defects, slows the disease progression, and extends the lifespans of mutant mice 2-3 fold in a dose-dependent manner. Our additional studies demonstrated that "substrate enhancement" therapy with dC+dT produces similar beneficial effects. Based on our preliminary *Tk2* knockin mouse studies, we obtained approval to treat a 19 month-old child with infantile-onset TK2 deficiency with dTMP+dCMP and then with dT+dC. Although still ventilator-dependent, the child has gained weight from 10.4 to 20.5 kg and increased limb strength; he has acquired the ability to stand for 5 minutes with support and use his hands to play with toys and use computers. More than 20 additional TK2 patients world-wide are taking dTMP+dCMP or dT+dC; all have shown clinical stabilization or increases in weight and strength. The therapy is currently being developed by a pharmaceutical company.

http://dx.doi.org/10.1016/j.nmd.2018.06.226

I.7
Development of genetic therapy for mtDNA diseases

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The human mitochondrial DNA (mtDNA) codes several proteins important for the function of the Oxidative Phosphorylation system (OXPHOS). These include 13 polypeptides, which are catalytic OXPHOS subunits, 22 tRNAs and 2 rRNAs. The mtDNA is inherited exclusively from the mother and it is present in multiple copies (approximately 1000 per cell). In the last 20 years, a large number of mutations (>200) in the mtDNA have been associated with clinical syndromes, affecting different organ systems. However, mutations in the mtDNA cause diseases only when the levels of the mutated genomes exceed a threshold that triggers a bioenergetics defect. Therefore, if the levels of mutant genomes could be reduced, the cell should recover its mitochondrial OXPHOS function. We have previously shown that we could use designer nuclease known as mitoTALENs to reduce the levels of the "common deletion" and several pathogenic point mutations in the mtDNA of cultured cells. To test whether this approach is effective *in vivo*, we developed mitoTALENs directed against a point mutation in the mtDNA of a heteroplasmic mouse model. This point mutation in the tRNA alanine gene (nt 5024 C>T) destabilizes the tRNA alanine, causing a mitochondrial protein synthesis defect in cells with high levels of the mutation. The two mitoTALEN monomers were expressed from AAV9 particles and injected in the Tibialis Anterior (TA) muscle of the right leg muscle. AAV9 coding for only one monomer was injected in the left TA. Mice were analyzed 6, 12 and 24 weeks after injection. DNA analysis showed a reduction in the percentage of mutant mtDNA in the right TA at all time points. The decrease in mutant mtDNA was variable between mice and it correlated with the amount of viral genomes expressed in muscle. In addition, we achieved systemic delivery and expression by retro-orbital injections of mitoTALENs. We are also developing monomeric mitochondrial nucleases based on homing endonucleases. We will be discussing the advantages and limitations of the different platforms.

http://dx.doi.org/10.1016/j.nmd.2018.06.227

NEW INSIGHTS INTO CELLULAR FUNCTIONS

O.7
Mitochondrial dysfunction triggers a pro-survival adaptive response through distinct DNA methylation of nuclear genes

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Epigenetics can modulate cellular responses to stress and DNA methylation has been associated to high intensity stress adaptive responses. We hypothesized that mitochondrial (MT) dysfunction could trigger an epigenetically mediated adaptive response. To test this, we studied stress responses in an *in vitro* and *in vivo* model of MT dysfunction and explored their epigenetic modulation. *In vitro:* human skeletal myoblasts exposed to the MT complex I inhibitor Rotenone(Rot) showed that high doses of the drug(Rot-1&10microM) managed to keep cell death to the control level, whereas lower doses(Rot-0.1microM) increased their cell death through apoptosis (AnnexinV+TO-PRO-3 flow cytometry). Autophagy was increased in the Rot-10microM condition (LC3 IIF+WB) and we proved that this process was necessary for cell survival. DNA methylation inhibition with 5-Aza-2′-deoxycytidine(5-Aza) evidenced that methylation was also necessary for this "pro-survival" state since cells showed enhanced apoptosis and inhibition of autophagy when treated with Rot-10microM+5-Aza. *In vivo*: Skeletal muscle and blood samples were obtained from MT disease patients and healthy controls. Autophagy was explored in muscle samples by LC3 WB revealing increased autophagy in patients. DNA methylation assays of tumor suppressor genes (MS-MLPA) was enhanced in both of patients' tissues. Reduced representative bisulfite sequencing(RRBS) also evidenced hypermethylation of CpG rich regions in patients' muscles. With G.R.E.A.T analysis of the RRBS data, we found that the pathways altered by distinct methylation correlated with the ones known to be dysregulated at a transcriptional level. Therefore, the transcriptome could be driven by DNA methylation in this MT dysfunctional scenario. We highlight the methylation and transcriptional alteration of the "Nutrient sensing network" key for autophagy and cell survival regulation. MT dysfunction leads to a "pro-survival" response that seems to be triggered by the differential methylation of nuclear genes.

http://dx.doi.org/10.1016/j.nmd.2018.06.228

O.8

SEPN1-related myopathy is a systemic metabolic disease: selenoprotein N maintains endoplasmic reticulum-mitochondrial interaction and regulates mitochondrial bioenergetics

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SEPN1-related myopathy (SEPN1-RM) is a potentially-lethal congenital muscle disorder due to mutations of *SELENON* (formerly *SEPN1*), encoding selenoprotein N (SEPN1). We reported that SEPN1 absence leads to oxidative stress which is restored ex vivo by the antioxidant N-acetylcysteine (NAC), but the precise function of SEPN1, a putative enzyme of the endoplasmic reticulum, remained unknown. Thus, SEPN1-RM has no treatment, and clinical trial readiness is hindered by the lack of biomarkers and outcomes. Using *in vitro* and *in vivo* murine models of SEPN1 deficiency as well as muscles and cultured fibroblasts from SEPN1-RM patients, we identified a radical decrease in ATP production and oxygen consumption and an *in vivo* metabolic phenotype suggesting that SEPN1 controls mitochondrial bioenergetics. Furthermore, we identified that SEPN1 is enriched at the MAM (mitochondria-associated membranes), and is needed for maintaining calcium transients between the endoplasmic reticulum and the mitochondria, as well as for the integrity of the reticulum-mitochondria contacts. This new role of SEPN1 can contribute to explain the fatigue and the abnormalities in fatty tissue and BMI observed in patients, which we have found correlate significantly with the severity of the muscle dysfunction and weakness. Our results reveal a novel role of SEPN1 in mitochondria regulation, identify a metabolic/systemic component in SEPN1-RM and define mitochondria as a novel therapeutic target, paving the way for identification of biomarkers and investigation of other potentially-therapeutic drugs. Also, our results contribute to understand the interplay between mitochondrial bioenergetics, the sarcoplamic reticulum and redox homeostasis in skeletal muscle, thus helping understand and potentially treat other redox-related or unrelated muscle conditions (such as muscular dystrophies, cachexia or sarcopenia).

http://dx.doi.org/10.1016/j.nmd.2018.06.229

O.9

Dysfunctional mitophagy: a potential therapeutic target in inclusion body myositis

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Inclusion body myositis (IBM) is the commonest acquired myopathy in adults over 50 years of age. There is no established treatment. Aetiology and pathogenesis are unknown. Diagnosis is based on clinical presentation supported by pathological findings. The combination of protein aggregates and mitochondrial changes in the muscle in IBM suggest that autophagy, a process for recycling damaged cellular components, is defective. Autophagy that recycles mitochondria is called mitophagy. To test our hypothesis that dysregulated mitophagy plays a key role in IBM we studied samples from patients with IBM (n=26) and aged-matched controls(n=39). Muscle mitochondrial DNA (mtDNA) copy number and mtDNA deletions were assessed by Q-PCR and long-range PCR. Fibroblasts were studied using high content imaging (INCell 1000). Energetic stress was achieved by using low glucose media. Mitochondrial membrane potential was assessed using tetramethyrhodamine dye. Mitochondria were evaluated by staining with antibodies to the outer mitochondrial membrane protein TOM-20. Mitophagy was determined by the colocalisation of TOM-20 and autophagosome marker LC3-II. We found that mtDNA copy number was lower in patients with IBM than controls. IBM samples with the lowest mtDNA copy number had greater numbers of cytochrome oxidase negative fibres and more variable mtDNA deletions. High content imaging revealed that fibroblasts from patients with IBM grown under energetically stressful conditions had i) reduced mitochondrial membrane potential, ii) increased mitochondrial volume, and iii) increased colocalisation of mitochondria and autophagosomes. Our findings of increased numbers of damaged and dysfunctional mitochondria in fibroblasts from patients with IBM indicate that mitophagy may be dysregulated. More work is needed to confirm these findings. However, if confirmed, it is possible that drug modulators of mitophagy may improve mitochondrial quality and affect disease progression in IBM.

http://dx.doi.org/10.1016/j.nmd.2018.06.230

O.10

The nuclear-cytoskeleton connection and nuclear positioning during muscle formation

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Muscle cells are characterized by the presence of multiple nuclei evenly spaced under the plasma membrane. Whether this particular arrangement is required for muscle function is still under debate. Nonetheless, several muscular diseases are characterized by abnormal nuclear positioning, such as centronuclear myopathies, titinopathies and desminopathies or due to mutations of nuclear envelope proteins known to be involved in nuclear movement in other systems. The position of nuclei could be important for proper distribution of mRNA and proteins in such large cells. We have, since several years, investigated the mechanisms controlling three of the four different and successive nuclear movements occurring during myofiber formation through live imaging. We have developed cell systems which can achieve myofiber maturation, with peripheral nuclei and presence of triads and sarcomeres. By

screening the effect of different molecular motors deletion, we have identified several microtubule-associated motors implicated at different levels on nuclear movement and positioning. We have established the connection between the nucleus and the cytoskeleton to be decisive for proper nuclear positioning. In particular, nesprin-1, a protein mutated in congenital muscular dystrophy, is required for the reorganization of the microtubule cytoskeleton during the differentiation of muscle cells and the subsequent nuclear movements. Anchored to the nuclear envelope, nesprin-1 is part of the LINC complex, making the link between the cytoskeleton and the lamins inside the nucleus. Our research using *in vitro* systems recapitulates *in vivo* observations and allow the study of the impact of mutations found in muscular diseases on nuclear positioning in muscle cells.

http://dx.doi.org/10.1016/j.nmd.2018.06.231

O.11

Secretion of toxic exosomes by muscle cells of ALS patients

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As several studies have shown that motor neuron degeneration starts at the neuromuscular junction and as we have previously shown that skeletal muscle can have a functional secretory activity, we hypothesized that communication between muscle and nerves is altered in ALS, and that the release from muscle of vesicles such as exosomes could have a key role in ALS pathogenesis. Muscle stem cells were extracted from the deltoid muscle biopsies of sporadic ALS patients and aged-matched healthy subjects (n=20 per group). Human Pluripotent Stem Cells were converted into pure populations of spinal motor neurons as previously described. Exosomes from ALS and healthy muscle cells were extracted using exosome kit (LifeTechnologies®). In muscle of sporadic ALS patients, we observed multi-vesicular bodies that are filled with exosomes (1.40 +/- 0.14 exosomes/mm2 in ALS, 0.9 +/- 0.07 exosomes /mm2 in control), and cultured ALS muscle cells have massively increased exosome content (RT-qPCR and immunostaining) and release 2-fold more exosomes. These exosomes are toxic to both muscle cells and motor neurons as once added to the culture medium of healthy muscle cells or of healthy motor neurons, they induced: Muscle fiber atrophy, cellular stress by stimulating blebbing, and cell death of muscle cells and motor neurons. When ALS exosomes were added to the culture medium of a human muscle cell line that over-expressed a tagged form of wild-type FUS (FUS-FLAG), they induced markedly greater cell stress and death than when added to SOD1-FLAG or TDP43-FLAG cell lines. These data suggest an interaction of ALS exosome content with FUS. Interestingly, FUS is aggregated in the nuclei of ALS muscle cells. Taken together, these data suggest that muscle cells from sporadic patients secrete toxic agents through their exosomes agents that interact with the FUS pathway. These exosomes may have a key role in the pathology of ALS.

http://dx.doi.org/10.1016/j.nmd.2018.06.232

O.12

Eccentric contraction causes loss of microtubule lattice organization in mdx skeletal muscle expressing mini- or micro-dystrophin

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Absence of dystrophin protein causes Duchenne muscular dystrophy, which is modeled by the dystrophin deficient mdx mouse. Compared to wildtype muscle, dystrophic mdx muscle is highly susceptible to eccentric contraction induced torque loss. Lack of dystrophin also influences the subsarcolemmal microtubule lattice. Wildtype muscle has a highly organized microtubule lattice of 90° intersections which becomes disorganized in mdx. Three additional mouse lines with disorganized microtubules are also susceptible to eccentric contraction induced torque loss, insinuating that microtubule lattice aberrations may contribute to the susceptibility of dystrophic muscle to eccentric contraction. Expression of mini- or micro-dystrophin transgenes in mdx skeletal muscle significantly rescues both eccentric contraction susceptibility and microtubule disorganization. Here we show that eccentric contractions can themselves also influence the microtubule lattice. While microtubule lattice organization of mdx muscle is significantly improved by any dystrophin transgene containing the N-terminus and cysteine rich domain, full lattice restoration requires either dystrophin spectrin like repeats R4-15 or R20-23. Mini-dystrophins containing R20-23 but lacking R4-15 can completely restore the microtubule lattice, however, micro-dystrophins lacking both regions only intermediately restore the lattice. Further, a chimeric dystrophin containing R4-15 but lacking R20-23 via substitution of homologous utrophin repeats, is also capable of restoring the microtubule lattice completely. Most interestingly, we find that both R4-15 and R20-23 appear to be required to fully protect the microtubule lattice from eccentric contraction. Lack of either dystrophin R4-15 or R20-23 results in partial transverse microtubule loss, and lack of both regions results in almost complete transverse microtubule loss while wildtype muscle suffers no microtubule loss after eccentric contraction.

http://dx.doi.org/10.1016/j.nmd.2018.06.233

NEW THERAPEUTIC APPROACHES

I.8

Emerging therapeutic approaches for Facioscapulohumeral muscular dystrophy (FSHD)

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Autosomal dominant Facioscapulohumeral muscular dystrophy (FSHD) is among the most prevalent muscular dystrophies, affecting 1 in 8,333 to 1 in 20,000 individuals. The clinical features of FSHD were first described in the 1800's, and the disease was formally classified as a major form of muscular dystrophy in 1954, but the pathogenic mechanisms underlying FSHD have only begun clarifying during the last decade. This lag in understanding can be largely attributed to the complicated nature of FSHD pathogenesis. Importantly, FSHD has now been linked to de-repression of the toxic *DUX4* gene in muscle. The emergence of *DUX4* represented a momentum shift in the FSHD field as it facilitated the development of cell and animal models and provided a target for rational therapy design centered on inhibiting DUX4 expression or activity. In this session, several newly emerging FSHD-targeted therapeutic strategies will be discussed, as well as possible paths forward toward clinical development.

http://dx.doi.org/10.1016/j.nmd.2018.06.234

I.9

Treatment of Duchenne muscular dystrophy: current efforts, bottlenecks and future prospects.

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In the last decade a number of therapeutic approaches for Duchenne muscular dystrophy has become available and there has been a proliferation of clinical trials.. Several initial approaches have focused on attempts to restore dystrophin production by targeting specific groups of mutations. These have focused out of frame deletions with antisense oligonucleotides, or nonsense

mutations with drugs allowing partial read through. These attempts have led to the first drugs to be commercially available but have also raised a number of questions on trial design and on the need to further explore aspects related to inclusion criteria, duration of the study and outcome measures used. Other approaches have targeted different aspects of the pathophysiology of Duchenne. As an alternative to dystrophin restoration, another approach focuses on the use of small molecuiles aiming to upregulate the production of a dystrophin like protein, utrophin. Others are aiming to target additional aspects such as reducing fibrosis, inflammation or degeneration or increasing muscle mass. Each of these aspects is at the moment currently studied in clinical trials. In the last years there has been increasing attention to gene therapy. Several attempts are being developed and the possibility to fit a highly internally deleted minidystrophin gene into an AAV vector is already part of a clinical trial. Other attempts following the same line are also in process and increasing attention has been devoted to the possible use of other methods.

http://dx.doi.org/10.1016/j.nmd.2018.06.235

NEW THERAPEUTIC APPROACHES AND THEIR READOUT

O.13

Genome editing for Duchenne muscular dystrophy

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The advent of genome editing technologies, including the RNA-guided CRISPR/Cas9 system, has enabled the precise editing of endogenous human genes. We have applied these tools to the correction of mutations that cause genetic disease. For example, we engineered CRISPR/Cas9-based nucleases to correct the human dystrophin gene that is mutated in Duchenne muscular dystrophy patients. When we delivered these nucleases to cells from patients with this disease, the correct gene reading frame and expression of the functional dystrophin protein were restored *in vitro* and following cell transplantation into mouse models *in vivo*. When delivered directly to a mouse model of this disease, gene editing by the CRISPR/Cas9 system led to gene restoration and improvement of biochemical and mechanical muscle function. More recently, we have developed novel animal models of this disease for the preclinical development of therapies that will correct human disease-causing mutations. New constructs have been developed and validated to have significant activity levels in this model, and improve the dystrophic phenotype of these mice. These studies demonstrate the potential for genome editing to be used to treat Duchenne muscular dystrophy and other neuromuscular disorders.

http://dx.doi.org/10.1016/j.nmd.2018.06.236

O.14

A mutation-independent approach via transcriptional upregulation of a disease modifier gene rescues muscular dystrophy *in vivo*

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Targeting disease modifier genes is an attractive therapeutic strategy in cases where causative genes are large and mutations are heterogeneous. Here, we report a mutation-independent strategy to upregulate expression of a compensatory disease-modifying gene in congenital muscular dystrophy type 1A (MDC1A) using a CRISPR/dCas9-based transcriptional activation system. MDC1A is caused by nonfunctional laminin $\alpha 2$, which compromises muscle fibers stability and axon myelination in peripheral nerves. Transgenic overexpression of *Lama1*, encoding a structurally similar Laminin $\alpha 1$, ameliorates muscle wasting and paralysis in MDC1A mouse models, demonstrating its role as a protective disease modifier. Yet, upregulation of *Lama1* as a postnatal gene therapy is hampered by its large size, which exceeds the genome packaging capacity of clinically relevant adeno-associated viral vectors (AAVs). In this study, we sought to upregulate Lama1 using CRISPR/dCas9-based system, comprised of catalytically inactive Cas9 (dCas9) fused to VP64 transcriptional activation domains and sgRNAs targeting the Lama1 promoter. We demonstrated robust upregulation of Lama1 in myoblasts, and following AAV9-mediated intramuscular delivery, in skeletal muscles of dy2j/dy2j mouse model of MDC1A. We then assessed whether systemic upregulation of *Lama1* would yield therapeutic benefits in dy2j/dy2j mice. When the intervention started early in pre-symptomatic dy2j/dy2j mice, Lama1 upregulation prevented muscle fibrosis and hindlimb paralysis. An important question for future therapeutic approaches concerns the therapeutic window and phenotypic reversibility. This is particularly true for muscular dystrophies as it has long been hypothesized that fibrotic changes in skeletal muscle represent an irreversible disease state that would impair any therapeutic intervention at advanced stages of the disease. Here, we demonstrate that dystrophic features and disease progression were significantly improved and partially reversed when the treatment was initiated in symptomatic 3-week old dy2j/dy2j mice with already-apparent hind limb paralysis and significant muscle fibrosis. Collectively, our data demonstrate the feasibility and therapeutic benefit of CRISPR/dCas9-mediated modulation of a disease modifier gene, which opens up an entirely new and mutation-independent treatment approach for all MDC1A patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.237

O.15

Humoral and cell mediated immune response to new dystrophin after morpholino-induced exon skipping therapy in dystrophin-deficient mdx mice

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Exon skipping is a promising genetic therapeutic strategy for restoring dystrophin expression in the treatment of Duchenne muscular dystrophy (DMD). The potential for newly synthesized dystrophin to trigger an immune response in DMD patients, however, is not well established. We have now evaluated the effect of chronic morpholino (PMO) treatment on skeletal muscle pathology and asked whether sustained dystrophin expression elicits a dystrophin-specific autoimmune response. Here, two independent cohorts of dystrophic mdx mice were treated with either 800mg/kg/month PMO for 6 months (n=8) or 100mg/kg/week PMO for 12 weeks (n=11). We found circulating antibodies directed against *de novo* dystrophin in 38% of the high-dose monthly PMO-treated cohort and 55% of the low-dose weekly PMO-treated cohort, as assessed both by Western blotting and immunofluorescent staining; however, no dystrophin-specific antibodies were observed in the control saline-treated mdx cohorts or in aged mdx mice with expanded "revertant" dystrophin expressing fibers. Further, anti-dystrophin IgG antibodies recognized both full-length mouse dystrophin (normal) as well as Becker-like truncated dystrophin protein (exon-skipped) in muscle. Finally, we show that antigen specific T cell interferon gamma, TNF-alpha and IL-6 production results from *de novo* dystrophin expression. More importantly, we found $CD8^+$ Cytotoxic T-cells in the vicinity of Major Histocompatibility Complex (MHC) class -1 and dystrophin positive muscle fibers. Our results show that *de novo* dystrophin expression in response to exon skipping triggers both humoral and cell mediated immune responses in mdx mice. The implications of these findings for the long-term success of exon-skipping therapy without immunosuppression are still unknown. Our data highlight the need to further investigate the nature and magnitude of the autoimmune response to newly synthesized dystrophin after exon-skipping therapy.

http://dx.doi.org/10.1016/j.nmd.2018.06.238

O.16

Myostatin expression is a reliable and quantifiable biomarker to monitor dose-dependent drug response in muscular dystrophy

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Currently there is no cure for muscular dystrophies but recently but promising treatments have emerged, highlighting the need of robust biomarkers. Several biomarkers have been proposed but none of them can monitor drug response longitudinally in a dose-dependent fashion. We recently demonstrated that in an atrophic muscle process, including muscular dystrophies, the myostatin pathway is intrinsically down-regulated to counter balance muscle wasting. This process was reversible in *MTM1*-deficient myotubular myopathy upon gene transfer leading to reactivation of the myostatin pathway. Here we show that components of the myostatin pathway are robust and reliable circulating biomarkers of drug efficacy in a gene therapy approach for dystrophin deficiency. Using an AAV8-microdystrophin vector in the GRMD dog model of Duchenne muscular dystrophy we demonstrate that the intrinsic loss of myostatin production in GRMD muscle can be partially corrected by AAV8-microdystrophin transfer in a dose-dependent manner. Importantly, and in agreement with the partial rescue provided by a micro-gene transfer approach, circulating myostatin levels in treated GRMD never reached WT levels. Two-year follow-up further demonstrated a decrease of circulating myostatin levels after high-dose treatment later in the disease course. Myostatin levels are thus the first quantifyable biomarker allowing for the non-invasive monitoring of treatment efficacy by providing a measure, which can determine the overall degree of the gene therapy efficacy as well as a longitudinal monitoring tool to follow eventual decrease of the therapeutic effect. This biomarker may therefore be also useful in future to judge the effect of combined therapy approaches non-invasively. Because circulating myostatin levels represent the product of general muscle health and activity we predict that myostatin pathway monitoring can be used to judge therapy efficacy in a wide range of neuromuscular diseases, which are associated with muscle wasting.

http://dx.doi.org/10.1016/j.nmd.2018.06.239

O.17

ASPIRO phase 1/2 gene therapy trial In X-linked myotubular myopathy: preliminary safety and efficacy findings

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XLMTM is a rare monogenic disease caused by mutations in the *MTM1* gene, characterized by profound muscle weakness, respiratory failure, and early death. ASPIRO is a Phase 1/2, open-label, randomized, ascending dose study to evaluate safety and preliminary efficacy of AT132 (rAAV8-*DeshMTM1*), an investigational gene therapy product for delivery of functional *MTM1* gene copies to skeletal muscle cells. The ASPIRO study plan is to randomize XLMTM patients less than 5 years of age into 3 ascending dose cohorts to receive a single intravenous (IV) administration of AT132 or to act as a delayed treatment control (DTC; n=1 per dose cohort). Cohort 1 treatment-randomized patients (n=3) received an IV infusion of 1×10^{14} vector genomes/kg of AT132. At time of data cut (6Feb18), individual patient follow-up ranged from 12 to 20 weeks. A total of 11 adverse events (AEs) were reported, of which 4 were deemed probably or possibly related to drug and 5 were deemed serious AEs (SAEs), including 1 SAE in the DTC patient and 4 SAEs in Patient 3, who responded to immunosuppression and supportive care. Changes from baseline to Week 12 for Patients 1, 2, 3, and 4 (DTC), respectively, in the CHOP-INTEND score were 27 (93%), 16 (36%), 9 (26%), and 3 (6%) points. Changes from baseline in the MIP have been 47 (142%), 46 (105%), 22.3 (86%), and -1.8 (-3%) cmH2O. Respiratory improvements resulted in the first treated patient being weaned off of ventilator completely, as compared with his baseline use of 12 hours BIPAP per day. All treated patients demonstrate increased limb and trunk strength; improved velocity, coordination, and accuracy of movement; and improved ability to communicate (increased loudness during vocalization and crying). In addition, there have been improvements in airway clearance, secretion management, and swallowing capability, to the extent that the first patient now tolerates oral food. Updated data will be presented at the 2018 WMS Annual Congress.

http://dx.doi.org/10.1016/j.nmd.2018.06.240

O.18

Significantly reduced muscle damage and inflammation observed in Duchenne muscular dystrophy patients following ezutromid treatment

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To share 48-week safety and efficacy results from PhaseOut DMD evaluating ezutromid, a potential first-in-class utrophin modulator for the treatment of all patients with Duchenne muscular dystrophy (DMD). PhaseOut DMD is a Phase 2 open-label study of ezutromid administered to 40 ambulatory patients with DMD. Primary endpoints (48 week) are magnetic resonance spectroscopy (MRS) assessments. Key secondary endpoints are evidence of target engagement and quantification of muscle damage in muscle biopsies at baseline (n=40) and week 24 (n=25) or 48 (n=15). Safety, pharmacokinetics, and functional measures are monitored throughout. At 24-weeks: MRS indicated a statistically significant decrease in water relaxation time (T2) in the soleus muscle: the average reduction was -0.86 milliseconds (95% confidence intervals -1.44, -0.28; n=38). There was a small increase in mean fat fraction (vastus lateralis: from 14.7% to 18.5%, n=37). A statistically significant reduction in %fibres expressing developmental myosin (MHCd) was observed; the average reduction was -2.61% (95% CI -4.33, -0.90) from mean baseline of 11.37%; a relative reduction of 23%. Mean utrophin intensity was maintained and even increased (relative +7%) (0.370 to 0.396, LSMD 0.026 95% CI, -0.005, 0.058). No patient lost ambulation and there were no meaningful changes in functional performance. All patients achieved ezutromid plasma levels sufficient to modulate utrophin. None of the patients had any clinically significant TEAE. These results suggest ezutromid continues to be safe and well tolerated. Final results of 48-week analysis will be presented. MRS T2 decreases in this age group are consistent with a reduction in muscle inflammation and/or damage. Decreased MHCd, a marker of regeneration, also indicates reduction in muscle damage. We anticipate that the 48-weeks results will support utrophin modulation as a safe treatment for DMD patients irrespective of their mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.241

O.19

First-in-human intrathecal gene transfer study for giant axonal neuropathy: review of safety, immunologic responses and interim analysis of efficacy

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Giant axonal neuropathy (GAN) is a rare childhood onset neurodegenerative disorder of the peripheral and central nervous system. Recessive *GAN* mutations cause loss of function of gigaxonin, a cytoskeletal regulatory protein, leading to progressive sensorimotor and optic neuropathy, CNS involvement and respiratory failure. We report on a single site, phase I, non-randomized, open label dose escalation gene transfer study for GAN (NCT02362438), a first-in-human intrathecal (IT) AAV9 mediated gene transfer trial for any indication. 9 GAN patients have been dosed at three dose levels (ranging from 3.5×1013vg to 1.8×1014vg) with scAAV9-JeT-GAN, with up to 2 year post-gene transfer follow up. We review safety and immunologic response to the gene vector and transgene (serum and CSF AAV9 neutralizing antibody titers, interferon-γ ELISpot analysis to GAN and AAV9 epitopes, CSF and peripheral cytokine analysis and white blood cell flow cytometry), and present an interim efficacy analysis. GAN natural history study data is used for comparison of outcome measures which include: Motor function measure 32 (MFM32), Neuropathy impairment score (NIS), Friedreich's Ataxia rating scale (FARS), myometry, grip and pinch strength, timed testing, electrophysiology, and neuroimaging. We highlight the overall safety and feasibility of an intrathecal route of AAV9 based gene transfer. The efficacy interim analysis highlights several key aspects: Feasibility for adequately targeting the nervous system, preferred IT dosing regimens needed for effective transduction, relevance of baseline neurologic impairment and disease progression in patient selection and stratification. This data also provides insight into the immunological implications of gene transfer with concomitant immunosuppressive regimens and their impact on AAV9 gene transfer safety and efficacy. This study is a proof of concept for IT gene transfer as a strategy for gene replacement targeting the central nervous system.

http://dx.doi.org/10.1016/j.nmd.2018.06.242

O.20

Results from ATB200-02: first-in-human, open-label, phase 1/2 study of ATB200 co-administered with AT2221 for Pompe disease

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Late-onset Pompe disease (LOPD) is caused by impaired lysosomal glycogen clearance due to acid alpha-glucosidase (*GAA*) deficiency. Accumulation of glycogen in skeletal muscle and diaphragm leads to loss of muscle and respiratory function. Recombinant human GAA enzyme replacement therapy (rhGAA ERT; alglucosidase alfa) is standard treatment for LOPD. ATB200-02 (NCT02675465) is a first-in-human, open-label, Phase 1/2 trial to evaluate ATB200, a next-generation rhGAA ERT, co-administered with AT2221, an oral pharmacological chaperone, in adults with LOPD. Twenty patients (pts) were enrolled: ERT-switch ambulatory (Cohort 1, n=11), ERT-switch nonambulatory (Cohort 2, n=4), and ERT-naive ambulatory (Cohort 3, n=5). Mean±SD 6-minute walk test increased for ambulatory ERT-switch (Month [Mo] 6 [n=10], +23.9±52.2; Mo 9 [n=10], +24.5±40.8; Mo 12 [n=8], +57.4±34.4 m) and ERT-naive pts (Mo 6 [n=5], +41.8±29.4; Mo 9 [n=5], +63.5±23.1; Mo 12 [n=2], +86.8±11.1 m). Other motor function tests were generally consistent with these results. Increases were observed in upper extremity strength in nonambulatory ERT-switch pts at Mo 6 and 9. Forced vital capacity (% predicted) increased in ERT-naive pts (Mo 6 [n=5], +4.2; Mo 9 [n=5], +6.2; Mo 12 [n=2], +6.0) and was generally stable in ambulatory ERT-switch pts (Mo 6 [n=9], -1.3; Mo 9 [n=9], -1.7; Mo 12 [n=7], -3.1). All cohorts demonstrated improvements in the Fatigue Severity Scale. ATB200/AT2221 was associated with reductions in creatine kinase and urine hexose tetrasaccharide. The most common treatment-emergent adverse events were upper and lower abdominal pain (n=8), diarrhea (n=8), and nasopharyngitis (n=6). Three events of infusion-associated reactions occurred in 550+ infusions. Data from this interim analysis show a clinical benefit of ATB200/AT2221 in ERT-naive pts and in pts who have been on ERT for ~5 years. ATB200/AT2221 has the potential to be a significant treatment alternative for patients with Pompe disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.243

DMD TREATMENT: ANIMAL MODELS

P.197

Antisense PMO treatment improves muscle recovery from fatigue after a novel *in situ* dynamic muscle contraction protocol in mdx mice

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The evaluation of muscle function is an important part of pre-clinical testing of novel treatments for muscular dystrophies. However, muscle pathology in the most commonly used mouse model of Duchenne muscular dystrophy (DMD), the mdx mouse, is less severe than that in DMD patients and most protocols only evaluate maximal isometric force (Fmax). In contrast, mdx mice on a DBA/2 background show significant muscle atrophy and may therefore be a better model of DMD pathology. We measured the force-frequency relationship, fatigue resistance during isotonic contractions at 30% of Fmax and resistance to eccentric contractions (ECC) in situ in the triceps surae (TS) of mdx and control mice on a BL/10 (5 m/o) or DBA/2 (3 m/o) background. In BL/10 mdx mice, Fmax was decreased compared to control mice (-17%), even though TS mass was increased (+50%). Specific force was decreased by 40-47% across the stimulation frequencies. Fatigue resistance was not different, but force recovery from fatigue was worse in mdx mice. In DBA/2 mdx mice the deficit in specific force was less (22-28%), but the deficit in Fmax was larger (-43%) compared to BL/10 mice due to muscle weight loss (-27%). Unexpectedly, fatigue recovery was better in mdx mice and we found no deficit during ECC. Dystrophin exon skipping was induced in a group of BL/10 mdx mice with antisense PMO. PMO treatment only improved specific force at high stimulation frequencies and the force deficit during ECC was only partially recovered. Force recovery from fatigue was normalised and muscle work during the protocol was increased. We believe it's important to evaluate muscle function during submaximal and dynamic muscle contractions and that our isotonic contraction protocol better resembles muscle usage *in vivo*. We suggest that the large deficit in specific force and the reduced recovery from fatigue of BL/10 mdx TS in situ might allow for the sensitive detection of the effects of novel therapies for DMD on muscle function.

http://dx.doi.org/10.1016/j.nmd.2018.06.245

P.198

Stabilised helical peptide-PMO conjugates improve dystrophin exon skipping in the heart of mdx mice

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Many novel therapeutic methods are being investigated for Duchenne muscular dystrophy. Importantly, an antisense oligonucleotide (AO) based

gene medicine to induce RNA splicing suppression leading to skeletal muscle re-expression of dystrophin has recently become an approved gene medicine. This AO chemistry, in which the ribose ring is substituted by a morpholino ring (phosphorodiamidate morpholino oligonucleotide [PMO]) results in a neutral backbone scaffold that is resistant to RNase-H nuclease degradation and does not elicit toxicity issues. However, the uncharged PMO backbone compromises serum protein binding and cellular uptake into target tissues, such as the heart. To facilitate cell uptake of PMOs, cell-penetrating peptides have been conjugated to PMOs. Unfortunately, the main property that enhances tissue transfection, i.e. a positively charged core (often arginine-rich) elicits membrane toxicity issues. We bring forward a platform technology whereby small peptides stabilised into a helical structure by stapling and stitching (two (stapled) or three (stitched) alpha, alpha-disubstituted, olefin-bearing amino acids are incorporated at defined positions during solid-phase peptide synthesis followed by all-hydrocarbon cross-linking) are conjugated to PMOs. We evaluated whether conjugation of a stabilised helical peptide could enhance the effectiveness of PMOs in a mouse model of DMD, the mdx mouse. We found that two daily intraperitoneal doses of peptide-PMO conjugate (50 mg PMO/kg bodyweight) led to a significantly increased induction of cardiac dystrophin expression compared to unconjugated PMO at the same molar dose. There was no difference in the number of dystrophin-positive fibres in the tibialis anterior and gastrocnemius muscles. We are currently developing and evaluating additional stapled peptide-PMO conjugates, which we believe could enhance antisense therapies aimed at many different diseases.

http://dx.doi.org/10.1016/j.nmd.2018.06.246

P.199

Microutrophin delivery shows phenotype improvement in mdx mice

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Duchenne muscular dystrophy (DMD) is a severe type of muscular dystrophy caused by mutation in the dystrophin gene and characterized by progressive muscle degeneration. One of the potential gene transfer agent for its treatment is an adeno-associated viral vectors (AAV). Utrophin, an autosomal homologue of dystrophin, can functionally compensate for the absence of dystrophin in DMD. Membrane expression of utrophin is detected in fetal myofibers but in adult mice it remains only in neuromuscular junctions. AAV-mediated delivery of utrophin to the mdx/utrn double-knockout mice showed improvements in dystrophic phenotype. The effect of exogenously delivered utrophin is not studied in mdx mouse model characterized by absence of dystrophin but not utrophin. The aim of this study was to control expression of AAV9-associated gene constructs after intramuscular administration and evaluate the effects of delivered agents on physiological parameters after intravenous administration of three types of microutrophin (human, human codon-optimized and murine) to adult mdx mice. To assess muscle function in mice we used hanging wire test and measured loss of force after lengthening contraction of hindlimb muscle. For expression verification and localization study we performed immunofluorescence analysis and western blotting. Two weeks after intramuscular administration in adult mice three types of microutrophins were detected in the sarcolemma. The maximum hanging time was 3-fold significantly increased five weeks after iv administration of human codon-optimized microutrophin and 2.5-fold increased after administration of murine microutrophin. Differences in force deficit after lengthening contraction and creatine kinase blood level were not detected. The most significant findings of this study was that AAV9-mediated delivery of human codon-optimized and murine microutrophin showed improvements in muscle strength of mdx mice.

http://dx.doi.org/10.1016/j.nmd.2018.06.247

P.200

Assessment of efficacy of a rAAV9-mini-dystrophin gene therapy candidate (PF-06939926) administered to aged DMDmdx rats

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We previously determined the effective dose of rAAV9-dys3978 (PF-06939926), a recombinant AAV9 vector expressing a human mini-dystrophin gene under the control of a muscle-specific promoter, administered intravenously to 2 months old DMDmdx rats. An extensive natural history assessment of the DMDmdx rat model also reported a more aggressive phenotype than the mdx mouse model in both skeletal and cardiac muscle tissues, which progressed unfavourably with age. To understand the range of disease severity over which PF-06939926 has the potential to impact disease, we administered this gene therapy candidate to DMDmdx rats at 4 and 6 months of age. All treatment groups were euthanized 3 months after treatment. Despite evidence of transduction efficiency similar to that seen previously in DMDmdx rats treated at 2 months, there was only a trend towards improved fibrosis in the biceps femoris, in the DMDmdx rats treated at 4 months old and little or no impact on the fibrosis in the diaphragm in this group or in both muscles in rats treated at 6 months old. Interestingly, fibrosis in the heart was significantly improved in the rats treated at 4 months old with non-significant trends for reduced fibrosis in the heart of rats treated at 6 months old. Importantly, functional efficacy in skeletal muscle as measured by the grip force test and in the heart by 2D echocardiography, was achieved in both groups. Greater strength and less fatigue were observed in the forelimbs of the DMDmdx rats treated at 4 months old, compared to the 6 months old treated group. In the heart, PF-06939926 effectively corrected DMD-related cardiac pathology and functional deficits in both 4 and 6 months old treated DMDmdx rats. In summary, together with the results from the 2 months old DMDmdx rat treatment study, these findings suggest that administration of PF-06939926 to younger DMDmdx rats induced a greater amelioration of the associated DMD tissue pathology and functional deficits compared to older DMDmdx rats receiving the vector. Importantly, the older rats remained responsive to the vector, especially in the heart. These data may assist in the design of future clinical trials with PF-06939926 in DMD patients with more advanced disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.248

P.201

Early insights from 'Of Mice and Measures', a collaborative project to improve models and methods for preclinical research in Duchenne muscular dystrophy, and its first focus on the D2.B10-*Dmd*^{mdx}/J (D2/*mdx*) and C57BL/10ScSn-*Dmd*^{mdx}/J (Bl10/*mdx*) mouse models

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Optimizing preclinical tools and methods to evaluate therapeutic candidates is critical to improve decision-making about advancing therapies to clinical testing. In collaboration with leading experts in the neuromuscular community and TREAT-NMD network, Charley's Fund, a patient-founded research nonprofit, organized an effort to address a timely topic of this nature: how to utilize a promising newer mouse model, the D2.B10-*Dmdmdx*/J (D2/*mdx*), which has been speculated to recapitulate human pathology better than the commonly used C57BL/10ScSn-*Dmdmdx*/J (Bl10/*mdx*). The group convened working groups and collected and analyzed D2/*mdx* and Bl10/*mdx* data from multiple academic and industry sources. Nearly 18,000 data points on mutant and WT strains were gathered spanning 10 labs worldwide, 650 individual mice, and 230 different functional, histological, imaging, biochemical and molecular parameters. In addition to information about best

practices and data gaps in the two models, the cross-lab data comparison yielded findings with broader implications. Even in labs of leading experts, notable differences in practices and results were identified. To begin, no single outcome was assessed across all 10 labs. Most commonly assessed was body weight in 6 labs, followed by serum creatine kinase in 5. 8 other measures were assessed in 3 labs, and another 16 in 2 labs. The effort also revealed: a) labs often use different protocols for the same measure; b) behavioral assessments in particular yield variable outcomes; and c) inconsistencies exist in control arm design and use of vehicle, sham, and untreated mice – for example 1/4 control mice in the aggregate dataset received vehicle but 3/4 received no treatment. This project highlights an important need to understand and address these differences to improve consistency, quality, and coordination of preclinical research in DMD – and a compelling opportunity to intervene early to organize effective research using the new D2/*mdx* model.

http://dx.doi.org/10.1016/j.nmd.2018.06.249

P.202

Low Kindlin-2 levels in patients and mouse model of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) occurs due to mutations in dystrophin, a part of the dystrophin-glycoprotein complex (DGC). This complex links the extracellular matrix (ECM) and the myofiber cytoskeleton, protecting the skeletal muscle against contraction-induced damage. Similar to the DGC, the integrin complex functions as a structural link between the ECM and the cytoskeleton, playing an important role in muscle fiber stability. In this complex, Integrin linked kinase (ILK) is responsible for signaling between the ECM and the muscle fiber. Kindlin-2 (also known as Mig-2/FERMT2) is physically attached to both integrin-and ILK proteins, thus it may serve as an anchor between the ECM and the inside of the cell in this integrin-kindlin-2-ILK complex. Gene expression profiling study at our laboratory has demonstrated that integrin complex molecules and ILK pathway are significantly increased in dystrophin deficient skeletal muscle from mdx mice, the DMD mouse model, and in children with DMD. Upregulation of these molecules occurs probably due to compensatory mechanisms for dystrophin deficiency. On the other hand, in our RNA-Seq and western-blot results, kindlin-2 is downregulated in the mdx mice and also in DMD boys' muscles, probably secondary to the dystrophic process in an unknown mechanism. Kindlin-2 is important for cell membrane integrity, via its interaction with the integrin complex as an alternative to the disrupted DGC, and for myogenesis, thus kindlin-2 may promote survival and regeneration in dystrophin deficient muscle. Further evaluation of kindlin-2 role in muscular dystrophy and as potential for therapeutic intervention is recommended.

http://dx.doi.org/10.1016/j.nmd.2018.06.250

P.203

Exons 6 and 7 skipping test on new murine model of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a severe genetic disease caused by different mutations in dystrophin gene. One of the promising treatment strategies which was already approved by Food and Drug Administration is exon-skipping. The approach is based on reading frame restoration after one or more exons exclusion from mRNA splicing. It is driven by specific antisense oligonucleotides (AON). We created new murine DMD model with deletion of exon from 8 to 34 and used it for exon-skipping approach test. In this particular case reading frame can be restored by simultaneous skipping of exons 6 and 7. We designed 6 antisense oligonucleotides for skipping of exons 6 and 7 and ordered vivo-morpholinos for better penetration through cell membrane. After *in vitro* tests on primary murine myoblasts derived from DMDdel8-34 mice two AON pairs were selected. It was shown on cell cultures, that individual AONs can induce corresponding exons skipping. Aim of the work was to check if vivo-morpholinos targeted to exon 6 and 7 skipping can induce reading frame restoration when injected together into muscles of model mice. Vivo-morpholinos B002+B009 and B002+B020 were injected together into tibialis anterior muscles of 8-week old DMDdel8-34 mice. 2 weeks after injection muscles were collected for RT-PCR, western blotting and immunohistochemistry analysis. It was shown that both combinations lead to exon 6 and 7 simultaneous skipping. At the same time other forms of mRNA with skipped exon 6 only or skipped exon 7 only were also detected. Western blot analysis didn't confirm shortened dystrophin isoform expression and no membrane staining was detected on treated muscle cryosections using antibodies against dystrophin C-terminus. For the moment it is not clear if protein absence can be explained by low mRNA level or such restricted dystrophin expression is downregulated by cellular mechanisms. Further experiments will be conducted to verify or negate dystrophin expression absence.

http://dx.doi.org/10.1016/j.nmd.2018.06.251

P.204

R-DMDdel52, a novel preclinical rat model of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD) is a neuromuscular muscle-wasting disorder that primarily affects boys due to a mutation in the dystrophin gene. DMD is caused by mutations that abolish the production of functional dystrophin protein, usually through frame-shifts or through nonsense mutations. Currently incurable, DMD is a prime candidate for exon-skipping based gene therapy approaches, due to the possibility to restore the disrupted open reading frame for DMD dystrophin transcripts. Due to the modular structure of the protein, the restoration of the reading frame allows the production of a partially functional dystrophin like those found in Becker Muscular Dystrophy (BMD) patients. BMD results from mutations that allow production of partially functional dystrophin protein. Importantly, BMD patients show a milder, sometime nearly detectable, and more slowly progressing, muscular dystrophy. The persistent failures to translate preclinical research done in mice to humans demonstrate the requirements for animal laboratory models accurately mimicking the human DMD disease condition. We have generated a Rat model for DMD that carries an exon 52 deletion (R-DMDdel52) leading to a complete lack of dystrophin protein, as a suitable preclinical tool for therapeutic approaches for the treatment of DMD disease. Since the large majority of DMD mutations (over 60%) are localized within the 45-55 exons region, this model can be considered as an appropriate preclinical tool for therapeutic approaches targeted at restoration of dystrophin expression by genome editing. R-DMDdel52 display many of the hallmarks of the disease, including increased centronucleation, fibrosis, and necrosis as well as the presence of regenerating fibres in uninjured muscle. The phenotype seems to be progressive with increasingly severe muscle weakness over time, as in human patients, indicating that this is a relevant preclinical model.

http://dx.doi.org/10.1016/j.nmd.2018.06.252

P.205

Effect of PDE5 inhibition on the post-contractile MRI blood-oxygenation-level-dependent (BOLD) effect in skeletal muscle of dystrophic mice

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Duchenne muscular dystrophy (DMD) is characterized by the absence of dystrophin, which is accompanied by lack of sarcolemma localized neuronal nitric oxide synthase (nNOSμ). This lack of nNOS impairs the ability to blunt sympathetic vasoconstriction and may reduce local blood flow following muscle contractions. To compensate for lack of nNOSμ, treatments with phosphodiesters-5a (PDE5a) inhibitors have been proposed. In this study we utilized the post-contractile MRI blood-oxygenation-level-dependent (BOLD) response as an *in vivo* marker of skeletal muscle microvascular function to test the hypothesis that a PDE5a inhibitor (sildenafil citrate) improves muscle oxygenation after muscle contractions in mdx mice. The peak post-contractile BOLD response was measured after five brief electrically stimulated tetanic contractions (2 s, separated by 3 min rest) of the lower hindlimb muscles performed in a 4.7 T Varian/Agilent MR system. Dystrophic mdx mice (C57BL/10ScSn-mdx) were treated with sildenafil citrate and compared to untreated mdx, nNOSμ-null, and wild-type mice (n=6/group). MR data were acquired (TR 2 s; effective TE 19 ms; axial slice thickness 1 mm) from the posterior compartment in the lower hindlimbs. The peak BOLD response following the muscle contractions was greater ($p<0.05$) in treated mdx (2.8±0.2%) and wild-type (3.3±0.3%) than untreated mdx (1.9±0.2%) and nNOSμ-null (1.7±0.1%) mice. Overall, the peak BOLD response was impaired in untreated mdx mice and nNOS-/-, but sildenafil citrate improved the BOLD response in mdx mice. These results support the use of PDE5 inhibitors to improve microvascular function following muscle contractions in muscular dystrophies lacking nNOS.

http://dx.doi.org/10.1016/j.nmd.2018.06.253

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Effects of sarconeos (API BIO101) on *in vivo* and *in vitro* models of Duchenne muscular dystrophy

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Duchenne muscular dystrophy (DMD), is an inherited muscular disease, characterized by progressive muscle weakness and cardiomyopathy leading to premature death. It is believed that DMD is notably characterized by a systemic mitochondrial defect central to disease etiology. Sarconeos (API BIO101) is a first in class Mas activator currently in clinical development (phase 2b) for sarcopenia. Twelve-week-old C57BL10-mdx mice were orally treated with vehicle or BIO101 at 50mg/kg*day for 8 weeks. Immortalized human skeletal muscle cells KM571 derived from DMD patient (exon 52 mutated) were also employed and treated with various doses of BIO101 ranging from 1 to 5 μM. Myoblast differentiation was investigated by fluorescent microscopy. Signalling pathways activation status was assessed by western blot. Oxygen consumption rate was measured using a Seahorse XF Analyzer. BIO101 treatment significantly improved physical performances of C57BL10-mdx mice when compared to vehicle-treated mdx animals: running distance (2.4-fold increase); TA muscle maximal isometric force (+ 15%, $p<0.01$). KM571 human myotubes exposed to BIO101 for two days displayed an improved basal and maximal mitochondrial respiration (+20% in OCR, $p<0.01$). Additionally, BIO101 stimulated KM571 differentiation according to increased myofibers diameter, number of nuclei per myotube and fusion index (+21%, $p<0.001$, +34%, $p<0.01$ and +7%, $p<0.01$, respectively) consistently with a rapid and significant activation of AKT/mTOR and MAPK signalling pathways both involved in muscle anabolism. Our study demonstrates that sarconeos (API BIO101), increases muscle performance consistently with improved mitochondrial respiration and anabolism. These results warrant further investigations notably on mitochondrial biogenesis and energy metabolism. Sarconeos, for which Orphan disease designation applications have been lodged could offer a new option, alone or in combination with gene therapies, for the treatment of DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.254

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Full-length but not truncated osteoprotegerin binds directly to muscle cells and increases rapidly dystrophic muscle force

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Clinical studies have shown that osteoporosis and muscle degeneration can occur in tandem following neuromuscular diseases. The receptor-activator of nuclear factor κB (RANK), the receptor-activator of nuclear factor κB ligand (RANKL), and osteoprotegerin (OPG) triad, a key pathway for bone regulation, is involved in Duchenne muscular dystrophy physiopathology. OPG, a decoy receptor for RANKL, the truncated (TR-OPG-Fc) or full-length OPG (FL-OPG-Fc) fused with an Fc fragment of IgG1 can inhibit RANKL/RANK interactions *in vivo* or *in vitro*. TR-OPG-Fc contains only 4 cysteine-rich RANKL domains while FL-OPG-Fc contains 4 cysteine-rich RANKL domains, 2 TRAIL death domains and 1 heparin-binding domain. We have shown that a 10 day treatment with FL-OPG-Fc during the first acute phase of degeneration in dystrophin-deficient mdx mice completely restored force and resistance to eccentric contractions of fast-twitch muscle. Because FL-OPG-Fc was superior to muscle specific deletion of RANK or anti-RANKL, anti-TRAIL, TR-OPG-Fc treatments, we hypothesized that the heparin-binding domain found in FL-OPG-Fc interacts directly with muscle. WB and confocal microscopy demonstrated that FL-OPG-Fc, but not TR-OPG-Fc, binds to C2C12 myotube. We next showed that heparinase III, which cleaves heparan sulfate chains, reduces FL-OPG-Fc binding by 50%. To further support the importance of the heparin domain, FL-OPG-Fc was co-incubated with equal concentration of heparin, which abrogated by 85% its binding ability. Next, using ex vivo contractile properties of isolated fast-twitch EDL, we showed that a 24h FL-OPG-Fc treatment increased significantly the absolute and specific forces of dystrophic EDL. In conclusion, FL-OPG-Fc, through its heparin-binding domain, binds directly muscle cells and can rapidly increase absolute and specific maximal tetanic forces. Current investigations are directed towards a better understanding of the mechanisms by which FL-OPG-Fc improves dystrophic muscles.

http://dx.doi.org/10.1016/j.nmd.2018.06.255

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Therapeutic benefits of intravenous cardiac progenitor cell and exosome-based therapies in a mouse model of Duchenne muscular dystrophy

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Cardiosphere-derived cells (CDCs) are cardiac progenitor cells with anti-inflammatory, anti-oxidant, anti-fibrotic, and regenerative properties. These therapeutic actions of CDCs target pathways central to the pathology of Duchenne muscular dystrophy (DMD). We have recently shown that injecting CDCs directly into the myocardium of mdx mice resulted in profound phenotypic improvements in cardiac and skeletal muscle – findings that motivated the HOPE-Duchenne clinical trial. The protean effects of CDCs appear to be mediated by the secretion of exosomes (EXOs), which transfer noncoding RNA into recipient cells, modifying their function. CDC-secreted EXOs recapitulate the therapeutic benefits of CDCs when injected into the arterial circulation of mdx mice. Here, we aimed to explore the efficacy of CDCs and EXOs when delivered intravenously (IV) – a clinically innocuous method which would markedly facilitate product tolerability in patients, if successful. Compared to vehicle-treated mdx mice, CDC-treated mice could run further (421m ± 17 *vs* 299 ± 15, $p<0.0001$) and their skeletal muscles produced more force (diaphragm: 7.2N/cm2 ± 1.1 *vs* 4.8 ± 0.8, $p<0.05$; soleus: 11.8N/cm2 ± 0.6 *vs* 7.9 ± 0.7, $p<0.001$ soleus) 3 weeks after a single dose. CDCs delivered IV also improved global heart function: left ventricular ejection fraction by echo was 66% ± 1, *vs*. 50% ± 1 in controls ($p<0.0001$). These functional improvements coincided with marked reductions in inflammation, oxidant stress, and fibrosis, while recruitment of myogenic precursor cells was augmented in both heart and skeletal muscle. Pretreatment of CDCs with GW4869, an inhibitor of exosome biosynthesis,

attenuated the functional improvements. Conversely, a single dose of EXOs from human CDCs, also administered IV, reproduced the therapeutic benefits and regressed muscle pathology. These findings motivate the ongoing HOPE-2 clinical trial, which tests the effects of allogeneic CDCs delivered IV to late-stage DMD patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.256

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Dystrophin expression in the rat urinary bladder

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Micturition problems are often reported in Duchenne muscular dystrophy with changing symptomatology over time. Here we examined the potential aetiology of this developmental urinary dysfunction by analysing the expression of dystrophin in urinary bladder from 24 h-, two weeks-, four weeks- and six months-old rats. Regional and cellular dystrophin distribution was evaluated by immuhistochemical co-localization studies in adult urinary bladders. This learned that dystrophin was expressed in alpha-smooth muscle actin-positive cells and in some calcitonin gene-related peptide-positive neurons in the lamina propria. In contrast, the vimentin-immunoreactive interstitial cells and the protein gene product 9.5-immunoreactive urothelial layer did not express dystrophin. Expression levels were quantified by Western blotting and showed that dystrophin isoforms Dp140 and Dp71 were consistently expressed between all age groups. However, within each age group, the expression level of Dp71 was higher than that of Dp140. The observation that dystrophin is expressed in calcitonin gene-related peptide-positive neurons in the lamina propria of the urinary bladder may open a new therapeutic window to treat micturition problems in patients suffering from Duchenne muscular dystrophy. This furthermore underscores that this comorbidity may not just have a myogenic, but also a neurogenic origin.

http://dx.doi.org/10.1016/j.nmd.2018.06.257

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Dystrophin expression in the rat intestine

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Gastrointestinal dysfunction is highly prevalent in Duchenne muscular dystrophy (DMD) with increased symptomatology over time. DMD is caused by a mutation in the gene that encodes for the protein dystrophin. Dp71 is one of the dystrophin isoforms that has been described to be expressed in non-muscle tissue. However, its distribution in the intestine has not been studied in detail. Here we examined the potential aetiology in a physiological model by analysing the expression of Dp71 relative to alpha-smooth muscle actin (aSMA) in six anatomic regions of the intestine, i.e., duodenum, jejunum, ileum, caecum, colon, and rectum from neonatal (24-hours postnatal; n=3), and adult (six months-old; n=5-12) rats. Expression levels, quantified by Western blotting, showed a threefold higher Dp71 expression in the distal part (caecum, colon, rectum), compared to the proximal part (duodenum, jejunum, ileum) of adult rats. Neonatal rats showed a similar distribution pattern as observed in adults. Interestingly, in both neonatal and adult rats, aSMA levels of the proximal and distal part were similar. This observation suggests that the difference in dystrophin expression is not due to difference in smooth muscle cells. It is known that Dp71 plays an important role in clustering and anchoring ion and water channels (aquaporins) to the plasma membrane. The distal part of the intestine is known to be able to absorb more water and ions than the proximal part. Thus, differences in Dp71 expression between the proximal and the distal part may relate to their physiological function.

http://dx.doi.org/10.1016/j.nmd.2018.06.258

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Myostatin inhibition and growth factor treatment of pre- and post-disease onset mdx mice does not improve the phenotype coherently

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Muscular dystrophies are genetic disorders compromising muscular function and leading to muscular wasting. While several clinical trials have been testing safety and efficacy on promising treatments, no cure exists yet. In the past 15 years myostatin, a negative regulator of muscular mass, has been a major focus of treatment development as mice treated with myostatin inhibitors got larger muscles. Clinical trials have, however, not yet demonstrated a significant ameliorating effect of myostatin inhibition in patients with muscular dystrophy. In order to investigate if myostatin inhibition treatment could be improved by concurrently boosting the muscle regeneration with growth factors we treated 4-week (pre-onset) and 8-week (post-onset) old cohorts of the Duchenne muscular dystrophy mouse model, mdx, with myostatin inhibitor alone, with a growth factor cocktail and with the growth factor cocktail alone once a week for 12 weeks, while monitoring the body weight. At the end of treatment, isometric and eccentric force contraction ex vivo in extensor digitorum longus (EDL) and soleus was determined. The muscular mass was generally bigger in the treatment groups receiving myostatin inhibition with and without growth factors, but specific force overall did not improve. Treatment of post-onset mice demonstrated an improvement of muscular stress resistance compared to controls. Overall, there was no significant overall effect of the treatments, regardless of type and age initiated, compared to controls. These findings in the mdx mice, and absence of clinical improvement in human clinical trials, suggest that treating DMD by means of myostatin inhibition should be re-evaluated.

http://dx.doi.org/10.1016/j.nmd.2018.06.259

DUCHENNE MUSCULAR DYSTROPHY - GENETICS

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Mutational spectrum of the DMD gene in pediatric patients from an Argentinian referral center

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Dystrophinopathies are a group of X-linked recessive neuromuscular disorders caused by mutations in *DMD* gene, which include Duchenne muscular dystrophy (DMD), Becker muscular dystrophy, X-linked dilated cardiomyopathy and mild forms of the disease. Large deletions and duplications account for 70% of the mutations while small mutations are found in the remaining 30% of the patients. Molecular diagnosis is important since it has implications in disease prognosis, genetic counselling and treatment options. In this study, we describe the mutation spectrum in *DMD* gene in patients from a Paediatric Reference Hospital in Argentina. A total of 344 unrelated patients (336 males/8 females) were studied by MLPA technique. Sequencing of DMD gene by Sanger or next generation sequencing was performed in 66 patients with negative MLPA, clinical and muscle biopsy compatible with dystrophinopathies. Molecular diagnosis was achieved in 276 (80.23%) of the cases. Overall, large deletions were found in 178 (65%) of the patients with positive results, followed by point mutations (22%) and large duplications (11%). Six patients showed contiguous gene deletion (2%). Point mutations identified in 62 patients were distributed as follows: 28 nonsense mutations, 19 small out of frame deletions, 8 splice site mutations, 3 small out of frame duplications, 2 missense mutations, 1 in frame deletion and 1 insertion. Genotype-phenotype analysis revealed exceptions to the reading frame rule in 10.1% of the cases. The highest percentage of this exception was due to in frame mutations that result in DMD phenotype caused by mutations that encompassed the actin binding domain and part of the rod domain. In conclusion, the diagnostic algorithm used in the present study was accurate for the molecular diagnosis of dystrophinopathies; in addition,

this study provides data about phenotype characteristics and genetic profile in paediatric patients in our country.

http://dx.doi.org/10.1016/j.nmd.2018.06.260

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The DMD Italian network: reporting 2127 genetic diagnoses of referred dystrophinopathies, reflections and impact on care and personalized therapies

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Dystrophinopathies are allelic diseases caused by mutations in the dystrophin gene. DMD (generally out-of-frame mutations) and BMD (generally in-frame mutations) are the more frequent phenotypes, but dilated cardiomyopathy and mild to asymptomatic phenotypes also occur. Exceptions to the frame rule are also known. Genetic diagnosis of dystrophinopathies is complex and genotyping is currently mandatory both for accurate care including prevention and for eligibility in clinical trials. The DMD Italian network is composed by 11 centers offering dystrophin genetic analysis. 2127 patients were referred and genotyped. Among these, DMD were 59% and BMD 41% revealing a very high number of BMD phenotypes. Among DMDs, 58% carried deletions, 11% duplications and 30% small mutations. BMDs show 78% of deletions, 9% of duplications and 13% of small mutations. Notably, the percentage of small mutations in DMD is higher than those reported; similarly BMDs do show a very high number of deletions, and small mutations are more frequent than duplications. Among small mutations, 45% (DMD) and 33% (BMD) are nonsense; the 62,8 % of out-of-frame deletions is eligible for single exon skipping (17,8% for exon 53 skipping, 17% for exon 51 skipping, 16,6 % for exon 45 skipping, and 11,4% for exon 44 skipping). Among all diagnosed DMDs/BMDs, 10,5% remained orphan of a causative mutation. In these case revising the clinical diagnosis (especially the muscle biopsy results) is necessary, although this might also imply that atypical mutations may occur in a remarkable number of DMD and third level of genetic diagnosis (CGH or RNA profile) are needed. This very large patient cohort allows considerations about DMD/BMD mutation detection, mutation types percentage with repercussion on care and new therapies.

http://dx.doi.org/10.1016/j.nmd.2018.06.261

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Genetic profile of Chilean patients with Duchenne muscle dystrophy

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Duchenne muscle dystrophy (DMD), is a progressive muscular disease, inherited as a X link. Is caused by the mutations of the dystrophin gene. Deletions of one or more exons account for approximately 50-65%, duplications 5-10% and point mutations 20-25%. Analyze the genetic profile of patients with DMD through regular checkups at the pediatric neurology department of the San Borja Arriarán Hospital. Retrospective descriptive study. Analysis of clinical records of 41 patients in evaluation by DMD, excluding patients diagnosed prior to the year 2010, with only biopsy and/ or PCR (polymerase chain reaction) without alterations. 41 patients with clinical manifestations and/or muscle biopsy with markedly reduced or no detectable dystrophin immunostaining, were studied by PCR, MLPA (multiplex ligation probe amplification) and/or Sanger sequencing techniques. 27/41 (66%) of patients had large deletions, 20/27 had compromised exons 44-55, and 3/26 had compromised exons 3-7. The most frequent deletion was exon 50, followed by exon 49. 3/41 (7,3%) presented duplications, which all affected exon 2. 10/41(24,4%) of patients had a negative MLPA, but a compatible muscle biopsy. In 1/41, sequencing was performed, showing nonsense mutation, in exon 41. Our study of the genetic profile of chileans patients is similar to previously reported, deletions are the most frequent alterations. It should be noted that biopsy continues to be an important tool for confirming diagnostics, due to our countries limited access to sequencing techniques. Because of this, we can extrapolate and conclude that the large percentage of patients with compatible muscle biopsy and negative MLPA, could correspond to point mutations, which would then coincide with the published. Therefore, it is important to make genetic diagnosis advances thus giving us the possibility of integrating new therapies and the ability to offer genetic counseling.

http://dx.doi.org/10.1016/j.nmd.2018.06.262

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Genetic modifiers of Duchenne muscular dystrophy

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DMD is a severely progressive disease leading to loss of ambulation (LoA) and cardiomyopathy in the 2nd and 3rd decades of life. There is significant variability in disease onset, progression, age at LoA and cardiomyopathy; and this is important in the design of clinical trials. Loci independent of the *DMD* gene have been implicated in explaining part of this variability. The minor G allele of a single nucleotide polymorphism (SNP) in the SPP1 gene (rs28357094) has been associated with greater severity of progression. Other related SNPs are: *LTBP4* haplotype (rs2303729, rs1131620, rs1051303, rs10880), CD40 rs1883832 and *ACTN3* rs1815739. The aim of this study is to analyse genetic modifiers in a cohort of ~400 DMD boys from the UK NorthStar network. We used an Illumina HumanOmni5-4v1-1_A array. Quality control steps included sexcheck, missingness and heterozygosity rates. Statistical analysis was performed in R (survival package) and a log-rank test was used for analysing the relationship of the minor allele in *SPP1* SNP with time to LoA. 107 patients were genotyped. Age at LoA was available for 42. The presence of the minor G allele in the SPP1 SNP did not have a significant effect on age at LoA (log-rank p=0.256). Our interim analysis suggests that the SPP1 minor allele was not significantly associated with age at LoA. This could be due to small sample size or the lack of stratification of patients according to steroid treatment (as in previous studies). The analysis of genotyping of 233 additional samples is underway and outcome will be correlated with steroid treatment, age at LoA and onset of cardiomyopathy. Moreover, part this DMD cohort took part in a double blind randomized placebo-controlled study investigating bisoprolol and perindopril treatment as a preventative treatment of cardiomyopathy. This study has recently finished and we will correlate the cardiomyopathy features with the genetic data once the data are unblinded.

http://dx.doi.org/10.1016/j.nmd.2018.06.263

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Genetic carrier screening for Duchenne muscular dystrophy: the outcome of over forty years of genetic counselling on disease incidence in New South Wales Australia

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Duchenne muscular dystrophy (DMD), an X-linked recessive genetic disorder results in progressive muscle weakness, causing significant morbidity and mortality. Its incidence is approximately 1 in 5000 live male births. DMD is caused by mutations in the dystrophin gene, maternally inherited in approximately two thirds of affected boys. Female relatives have carrier risk. Clinical genetics services offer carrier testing ('cascade screening') and genetic counselling for relatives of DMD patients, enabling identification of carrier status and provision of reproductive options. In selected countries, reduced disease incidence is observed, possibly due to genetic counselling, cascade testing and prenatal diagnosis. To estimate changes in DMD incidence in NSW over 40 years and determine whether cascade screening and genetic counselling has led to this change. A retrospective study of 'probands' (live male and prenatal genetically diagnosed DMD) cases born within NSW from 2002-2012 will be conducted. Female carriers/mosaic cases are excluded from analysis. A retrospective clinical review of confounding factors potentially associated with DMD diagnosis will also be conducted, using clinical data sourced from all the major NSW paediatric hospitals. Data will be collated with results from a previous study reporting DMD incidence over a 25-year period from 1975 to 2001 inclusive. The combined results of these studies will be presented in the final analysis. Birth rate statistics will be sourced from the Australian Bureau of Statistics. The denominator for incidence will be live male birth rates. Data analysis is pending. However, we hypothesize that DMD incidence in NSW has reduced over the last 40 years owing to improvements in the methodology of genetic screening. This study will demonstrate the impact of robust genetic screening and counselling services, thus serving as a model for other health care systems globally.

http://dx.doi.org/10.1016/j.nmd.2018.06.264

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Duchenne and Becker muscular dystrophy carrier mothers: characterization of skeletal and cardiac muscle compared to healthy controls

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The risks of developing dystrophinopathy symptoms in female carriers have been linked to skewed X-chromosome inactivation with overrepresentation of the affected allele in the target tissue. Clinical manifestations reported include cardiomyopathy, skeletal muscle weakness and elevated creatine kinase (CK). The reported incidence of such abnormalities varies depending on the method of detection. We aim to prospectively assess the prevalence and extent of skeletal and cardiac muscle impairment in mothers of patients with Duchenne and Becker muscular dystrophy (DMD) in comparison to age-matched healthy controls. This longitudinal observational study characterizes skeletal and cardiac impairment in three cohorts: somatic carrier mothers, non-somatic mothers and age-matched healthy controls. Subjects from all cohorts are assessed at baseline and annually thereafter. To date, 95 subjects have been enrolled: 51 somatic carrier mothers, 18 non-somatic mothers and 26 healthy controls with mean ages of 43.1, 40.2 and 42.3 years respectively. Skeletal muscle weakness on manual muscle testing was detected in 25% of the somatic carriers compared to 17% in non-somatic mothers. Objective weakness was documented through reduced quantified knee extension strength (MVICT) only in the somatic mothers ($p<0.005$). Elevated CK was seen in 41% of somatic carriers. Late-gadolinium enhancement on cardiac MRI studies suggestive of myocardial fibrosis was observed in nearly half (46%) of the somatic carriers. Enrollment is continuing and additional data will be presented. This study corroborates reports of skeletal muscle weakness in manifesting carriers and provides greater detail than previously reported using cardiac MRI, permitting early detection of cardiomyopathy in somatic carriers. This novel study design is the first to assess all DMD/BMD mothers, carriers and non-carriers, with a healthy control arm to help distinguish manifestations due to age and daily burden of a caregiver.

http://dx.doi.org/10.1016/j.nmd.2018.06.265

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Heart and skeletal muscle affection in female carriers of a dystrophin gene mutation

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Female carriers of mutations associated with Duchenne (DMD) and Becker (BMD) muscular dystrophies are typically considered unaffected. However, different degrees of symptomatic carriers have been reported. Through an observational, prospective, cross-sectional study, female carriers of a *DMD* mutation were examined to investigate the frequency and extent of heart and muscle involvement. Genetically verified female carriers of a *DMD* mutation were examined by Magnetic Resonance Imaging (MRI) of the heart and the lower extremity muscles, by isokinetic muscle dynamometry of legs, echocardiography, 24-h Holter monitoring, ECG and blood concentrations of creatine kinase (CK) and cardiac biomarkers. Dixon MRI was used to determine muscle fat fractions of the lower extremity muscles and was correlated to muscle strength measurements. MRI late gadolinium enhancement was used to examine the presence of heart muscle fibrosis. A total of 52 subjects were included and data analysis is ongoing. We found that 71% of subjects had higher fat fractions (mean+2SD) than the 19 age- and gender-matched healthy controls in one or more lower extremity muscle groups. Subjects had significantly lower maximum voluntary force in dynamometry in all muscle groups. Fifty-six percent of subjects had elevated CK. Furthermore, the normal linear relationship between lean muscle mass and force, as seen in healthy controls, was not present in the carriers, indicating an overall contractile dysfunction of skeletal muscles. Preliminary cardiovascular results show that 11 of 48 subjects (23%) had reduced left ventricular systolic function. Female carriers of dystrophin gene mutations have higher fat fractions in skeletal muscles, lower maximal voluntary force, and impaired contractility of their lean muscle mass, compared to healthy controls. A subset of carriers had reduced cardiac contractility. Final results from both skeletal and heart muscle analysis will be presented at the conference.

http://dx.doi.org/10.1016/j.nmd.2018.06.266

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Duchenne and Becker muscular dystrophy carriers: emerging evidence for a clinically important cardiomyopathy

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This is a longitudinal prospective cohort study to define the incidence of cardiac disease in mothers of males with Duchenne/Becker muscular dystrophy. Mothers were determined to be a somatic or non-somatic carrier by genetic testing. Healthy volunteers were controls. 85 women underwent graded exercise treadmill evaluation with oxygen consumption measurement as well as a cardiac MRI (CMR) with gadolinium. 49 somatic carriers, 18 non-somatic carriers, and 18 controls with normal CK levels. Mean age 41.9 yrs (SD 8.41, range 28-63) did not differ among cohorts. Maximal oxygen consumption (VO2max) did not differ between somatic and non-somatic cohorts. However, a significant difference was noted between a combined somatic and non-somatic cohort (mean 28.9ml/min/m2, SD 6.9) when compared to control patients (34.9ml/min/m2, SD 3.7; $p=0.06$). Non-sustained ventricular ectopy during exercise testing was seen in 50% of somatic patients (25/49), which differed from non-somatic and control cohorts ($p=0.01$). Assessment of ventricular systolic function by CMR was normal in all cohorts. Sub-epicardial late gadolinium enhancement (LGE) was demonstrated in 47% (23/49) of somatic patients and 5% (1/18) of non-somatic patients ($p=0.0003$) and 0% in control subjects. Age was higher in those who demonstrated both ventricular ectopy with exercise (mean 44.2 yrs *vs*. 39.5 yrs, $p=0.041$) and LGE by CMR (mean 45.5 yrs *vs* 37.8 yrs, $p=0.004$). This is the first study to describe both abnormalities by treadmill testing and CMR fibrosis in a large group of somatic carriers. Low VO2max by exercise treadmill testing was consistent with deconditioning

and was independent of genetic mutation. Ventricular ectopy during exercise was more frequent in somatic carriers than either non-somatic patients or controls. This may represent occult cardiomyopathy. While systolic ventricular function is preserved, fibrosis is noted in half of the somatic cohort. Both ventricular ectopy and LGE was more prevalent with advancing age.

http://dx.doi.org/10.1016/j.nmd.2018.06.267

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A neuropsychological and neuroimaging study of female carriers of *DMD* mutations

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Dystrophinopathies are caused by *DMD* mutations and include Duchenne/Becker dystrophies. Men are typically affected, but subtle clinical signs have been increasingly reported in female carriers of DMD mutations (fcDMD) as well. Cognitive and cerebral abnormalities are major findings in affected men, but have not yet been assessed in fcDMD. Objectives: To investigate cognitive and neuroanatomical abnormalities in fcDMD. Fourteen fcDMD were submitted to neurological and neuropsychological examination, employing either the Addenbrooke's Cognitive Examination – Revised (ACE-R) test or the Montreal Cognitive Assessment (MoCA). For each subject, volumetric T1 cerebral sequences were obtained in a 3T MRI scanner. A control group of 14 age-matched healthy women was used for comparison. We computed cortical thickness measurements using the FreeSurfer software. Between-group comparisons were performed with GLM taking total intracranial volumes as covariates. Pearson coefficients explored associations between cognitive tests and MRI results. P values <0.05 were considered significant. Mean age and education of the fcDMD were 37.3 ± 6.4 years and 8.5 ± 3.6 years, respectively. None of the fcDMD presented muscular weakness or ECG abnormalities. Mean ACE-R and MOCA scores were 73.7 ± 9.6 and 24.5 ± 2.1. Half of patients ($n=7$) scored below the expected Brazilian and schooling-adjusted reference levels. Abnormal domains included attention/temporal orientation, language and visuospatial skills. MRI analyses revealed right inferior temporal cortical thinning in fcDMD, but it did not correlate with cognitive scores. fcDMD have cognitive and neuroanatomical abnormalities. Temporal regions look particularly vulnerable, but further studies are needed to fully characterize the structural pattern of damage in fcDMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.268

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Unsolicited findings in the *DMD* gene; what are the implications?

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Since the introduction of array analysis in molecular diagnostics for patients suffering from intellectual disability and/or developmental disorders as for prenatal diagnostics, many unsolicited findings were made. So far, about 40 different cases with possible implications for a dystrophinopathy have been reported to our centre. In these cases about an equal amount of gross deletions and duplications within the *DMD* gene were observed. In nearly all cases array results could be confirmed and deletions/duplications were accurately mapped by means of MLPA of the *DMD* gene. In at least 16 cases the mutations found may have implications for the patients and/or their families. In the majority of cases with duplications, no pathogenic effect was found by segregation studies in the family. Additional FISH analysis in some cases showed that duplications were located in other parts of the genome (outside the *DMD* locus or even outside the X-chromosome), and that a number of duplications extended towards both the 5′ or 3′ end of the *DMD* gene and even further; expecting to not disturb the normal DMD function. Most deletions, except for one, were internal gene deletions; identifying new dystrophinopathy patients and B/DMD carriers. In a few cases the identified mutations were not known in existing *DMD* databases, possibly indicating that these mutations might be harmless occurring in the general population. In two cases prenatal DNA analysis identified a male fetus with an out-of-frame deletion indicating a possible novel DMD patient. Unsolicited findings in the *DMD* gene identified by whole genome array analysis can be a challenge to interpret, especially if the identified variant is novel and the patient is too young to exhibit a dystrophinopathy phenotype yet. In most cases additional investigations are necessary to provide more clarity about the pathogenicity of the variant and to establish the implication for the patient.

http://dx.doi.org/10.1016/j.nmd.2018.06.269

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Influence of the intronic breakpoint of the *DYS* 45-55 exon deletion on the clinical phenotype

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Multiexon skipping is a novel approach in the treatment of DMD that can be achieved with the new Crispr-Cas9 technology. In particular, 63% of DMD mutations are located between exons 45 to 55 and spontaneous deletion spanning that region occurs in asymptomatic subjects or with variable Becker phenotype. We evaluate a cohort of subjects with a 45-55 deletion sustaining the hypothesis that intronic breakpoint positions might influence the phenotype. We analyzed the exact position of the del 45-55 intronic breakpoints in 10 index patients, first performing arrays and multiple PCRs to restrict the breakpoint areas, followed by amplification and sequencing of the junction deletions and the stretch spanning each breakpoint. Finally we reviewed the clinical and cardiac features. Seven patients shared the same breakpoints in both introns but presented variable clinical manifestation: 2 asymptomatic, 3 paucysymptomatics and two manifesting mild BMD phenotypes with associated cardiomyopathy in one of them. Two patients harbored a different deletion point that affected the regulatory regions of the dystrophin isoform Dp140. One of them manifested mild muscle symptoms (myalgia) with evident cognitive impairment. The other was asymptomatic but presenting an incipient dilated cardiomyopathy. The last patient showed a proximal insertion of a stretch from the deleted region in the 44-45 intronic breakpoint and manifested a BMD phenotype with an early onset cardiomyopathy. We cannot certainly affirm that the position of the intronic breakpoints in patients with deletion 45-55 is an absolute determinant of the phenotype, nevertheless we found several associations suggestive of some kind of influence.

http://dx.doi.org/10.1016/j.nmd.2018.06.270

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Small mutation detection in the *DMD* gene by whole exome sequencing of Argentine dystrophinopathy children

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Dystrophinopathies are neuromuscular X-linked recessive diseases caused by mutations in the *DMD* gene. The present study aimed to identify *DMD* gene small mutations by Whole Exome Sequencing (WES), in order to confirm clinical dagnosis, identify candidates for Premature Termination Codon (PTC) Read-through treatments and perform carrier status testing. Furthermore, was our goal to characterize the identified DMD sequence variants and determine the existance of co-segregating haplotypes. We analyzed 40 non-related individuals (38 affected boys and 2 at-risk women) with negative MLPA results. The WES and the implemented pathogenic variant selection algorithm probed to be efficient, showing a detection rate of ∼84% (32/38). We have found 15 nonsense mutations, 9 deletions/duplications and 8 splice site mutations. We could identify 15 PTCs read-through candidates and ex-

clude 2 at-risk women. The characterization of the occurrence and diversity of DMD sequence variants from our cohort and from LOVD database, revealed no hot spots but showed exons/introns unlikely to carry small molecular alterations and exons presenting a greater mutagenic abundance than others do. In addition, we have detected two co-segregating haplotypes blocks, which might have an european origin. Finally, this work represents the first *DMD* gene small mutations screening applying WES in an argentine cohort, contributes with the characterization of our population and collaborates with the DMD small mutation's background.

http://dx.doi.org/10.1016/j.nmd.2018.06.271

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Whole-genome sequencing reveals a complex intra-chromosomal rearrangement disrupting the dystrophin gene due to an intronic 0.5 Mb-insertion in a boy suffering from Duchenne muscular dystrophy

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The majority of DMD patients are affected by large intragenic mutations (deletions or duplications) or small mutations within coding regions. Only approx. 0,3 % of the DMD patients in Europe harbor intronic mutations, most of them are not captured by current diagnostic protocols. We report on a Polish boy, who was found to have elevated serum creatine kinase (CK) levels at the age of 3 months. Achieving his motor milestones was delayed and progressive muscle weakness finally confined him to wheelchair at age ten. At the age of 2, a muscle biopsy was performed in Poland, which was reported to lack dystrophin expression, whereas in a second muscle biopsy performed at the age of 8 in Vienna, expression of a dystrophin-protein harboring the N-terminus and parts of the rod-domain but lacking the entire C-terminus was detected. Molecular genetic analysis by MLPA did not yield any abnormalities. Subsequent RT-PCR sequencing of muscle RNA failed to amplify a fragment spanning exons 48 through 58, suggesting a complex rearrangement within the corresponding part of the DMD gene. As the causative mutation in this patient was still missing, we performed whole-genome sequencing (WGS), which revealed a hemizygous insertion of a large 0.5 Mb fragment into DMD intron 49, obviously resulting from a segmental duplication at Xp11.4 comprising the *ATP6AP2* and *MED14* genes. While leaving intact the complete coding region of the *DMD* gene, this mutation disrupts the gene on the transcript level and thus is compatible with absence of full-length dystrophin. To accelerate the establishment of the diagnosis of DMD and consequently rapid implementation of adequate therapy, WGS is indicated in patients with elevated CK, unambiguous clinical presentation and missing evidence of a pathogenic mutation in MLPA and DNA sequencing of the *DMD* coding regions.

http://dx.doi.org/10.1016/j.nmd.2018.06.272

CONGENITAL MYOPATHIES: NEMALINE AND TITINOPATHIES

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Clinical, genetic and neuropathological heterogeneity in a pediatric cohort with nemaline myopathy

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Nemaline myopathies are a vast group of rare muscle diseases sharing a common pathognomonic histological marker: nemaline rods - dark-blue structures visualized in muscle fibers stained with Gomori Trichrome. A pediatric cohort from a reference center in the north of Portugal (between 2002-2017) was reassessed. Eight patients (4 of each gender) with ages between 1 and 18 yrs were diagnosed. Two patients were siblings and other two had family history. Six had a neonatal presentation with tetraparesis, distal arthrogryposis, and severe axial and bulbar involvement, 4 required invasive ventilatory support and 4 tube feeding. One patient died with 3m of age. All 8 patients needed ventilation support and one performed scoliosis surgery. Five were able to walk between 18 and 72m (34m average). Muscle biopsy was reviewed in 5: rods, mainly in the periphery, variable proportion of affected fibers, without correlation with clinical severity. In terms of their genetic etiology, the most frequent defective gene in this cohort was nebulin (*NEB*) affecting 5 patients (1 homozygous and 4 compound heterozygous). Six distinct pathogenic variants in *NEB* gene were identified: 3 affecting splice-sites, 2 causing frameshift and 1 nonsense. All give rise to premature termination codons. Several unrelated patients shared at least one *NEB* variant meaning that these could be preliminary targeted in future cases. One patient has a *de novo* pathogenic missense variant in *ACTA1* gene. Finally, in the kindred with two affected siblings, a novel heterozygous missense variant in *KLHL41* gene was identified. Further research is being carried-out to identify an eventual missing variant that would justify an autosomal recessive inheritance pattern. Considering the variability presented here and the size of the patient cohort, no genotype-phenotype correlations were drawn. Nevertheless, the absence of cardiac involvement in this cohort is concordant with previous reports.

http://dx.doi.org/10.1016/j.nmd.2018.06.273

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Functional nebulin studies for assessment of pathogenicity

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The enormous nebulin protein (600-900 kDa) is located in the thin filament of the skeletal muscle sarcomere. It has a modular structure, consisting of actin-binding simple repeats. Seven simple repeats form one super repeat, each with a predicted binding motif for tropomyosin. To date, recessive pathogenic variants in the nebulin gene (*NEB*) are known to cause five myopathies, but the interpretation of the relatively common missense variants is difficult. Missense variants are well tolerated in *NEB*, and bioinformatic tools often fail to predict their effects. Therefore, it is essential to develop a functional tool for assessing the pathogenicity of missense variants. We hypothesised that one of the disease-causing mechanisms in *NEB*-related myopathies is altered interaction between nebulin and its binding partners. To investigate this, we selected 25 variants identified in patients, and expressed them in nebulin super-repeat fragments, alongside with the corresponding wild-type fragments. The binding of the nebulin super repeats to filamentous actin was determined using an *in vitro* co-sedimentation assay. We will expand the study to cover nebulin-tropomyosin interaction. This study showed that the *NEB* variants can alter nebulin-actin interaction, compared with the wild-type nebulin fragment. According to our preliminary results, six of the studied variants weakened the nebulin-actin interaction, while four of the variants strengthened it. Ten of the variants did not alter the interaction. The aim of this study is to obtain data to benefit diagnostics and development of future therapies. Furthermore, studies of individual protein interactions shed light on the function of the giant nebulin in the skeletal muscle sarcomere. We conclude that our functional assessment of *NEB* variants has been successful, and that altered interaction between nebulin and its binding partners may, indeed, act as a disease-causing factor in *NEB*-related myopathies.

http://dx.doi.org/10.1016/j.nmd.2018.06.274

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Unraveling muscle slowness in NEM6 myopathy: a key role for the skeletal muscle thin filament

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Nemaline myopathy (NM) is among the most common non-dystrophic congenital myopathies. Recently, a novel implicated gene was discovered - *KBTBD13*. NM patients with mutations in *KBTBD13* (NEM6) exhibit muscle weakness and a typical muscle slowness. Here, we aim to gain insight in the pathophysiology of NEM6 myopathy muscle slowness. *In vivo* muscle relaxation was assessed using Transcranial Magnetic Stimulation (TMS) in NEM6 patients (n=10) and controls (CTRL) (N=24). Contractile parameters were measured in isolated single fibers and in myofibrils that were isolated from skeletal muscle biopsies. Next, the nanoscale structure and acto-myosin interactions in these muscle fibers were studied by X-ray diffraction. *In vivo* TMS revealed slower muscle relaxation in NEM6 patients. Relaxation kinetics of both single muscle fibers as well as individual myofibrils were slower in NEM6 compared to CTRL. X-ray diffraction studies show that the peak position of the actin layer line 6 was reduced in NEM6 compared to CTRL, suggesting a compressed, stiffer thin filament. Modelling of sarcomere kinetics revealed that a stiffer thin filament slows muscle relaxation. Here, we studied the pathophysiology of muscle slowness in NEM6 patients. We used a top-to-bottom approach: from the patient *in vivo* level to the nanoscale acto-myosin *in vitro* level. The data suggest that changes in the skeletal muscle thin filament level contribute to the clinical phenotype of NEM6.

http://dx.doi.org/10.1016/j.nmd.2018.06.275

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Severe nemaline myopathy manifesting as 'Amish phenotype' related to homozygous mutation in *TNNT1*

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Amish nemaline myopathy is a severe form of nemaline myopathy (NM) common among the old order Amish. The phenotype is characterized by early onset of severe hypotonia and mild contractures of the shoulders and hips. Progressive worsening of the proximal contractures, weakness, and a pectus carinatum deformity develop before the children die of respiratory insufficiency, usually by the second year of life. This phenotype has been associated to the p.Glu180Ter mutation in exon 11 of *TNNT1* (TnT). We report on two Italian siblings affected by a severe form of congenital myopathy with a clinical picture very similar to the Amish phenotype. Both girls actually aged 12 and 1 years, by the age of 3 months, started to manifest rapid and progressive muscle weakness that predominantly involved distal muscles, associated to severe chest deformity (pectus carinatum) rigid spine and respiratory insufficiency that required mechanical ventilation in the first year of life. A muscle biopsy, performed in the older sister at the age of 7 months was consistent with a NM. Next generation sequencing approach revealed d a biallelic c.661G>T mutation in exon 12 of *TNNT1* converting the Glu221 to a premature stop codon. The deletion of the C-terminal 58 aminoacids of TnT causes a loss of the binding sites for the Troponin inhibitory subunit (TnI) and the Troponin Ca2+-binding subunit (TnC) in the T2 region of TnT. The phenotype described in the Amish community is not a distinct myopathy associated exclusively to the founder Glu180Ter *TNNT1* mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.276

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Genetics and modeling of *TNNT1* genetic variants in nemaline myopathy

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TNNT1-related nemaline myopathy (NEM5) comprises a small but increasingly significant cause of nemaline myopathy. Initially described as a severe autosomal recessive condition confined to the Old Order Amish of Pennsylvania in the US, subsequent patients with severe phenotypes have been described throughout the world. The prototypic clinical features include congenital hypotonia and weakness of proximal, bulbar, facial, and neck flexor muscles that may result in death secondary to respiratory insufficiency. This condition appears to exhibit allelic heterogeneity with multiple mutations within the same gene causing the severe recessive form of the disease. We recently described the first autosomal dominant c.311A>T, p.E104V pathogenic variant of *TNNT1* gene occurring in an Ashkenazi Jewish family in the United States. This family had an overall milder phenotype than the recessive cases with marked clinical heterogeneity ranging from a Gower's maneuver in childhood to mild difficulty weight training late into adulthood. Recent whole exome sequencing studies in a large cohort of congenital myopathy cases have identified two additional unrelated cases with potentially pathogenic dominant *TNNT1* mutations as well as two new instances of possible recessive variants. To assess pathogenicity of these variants we are establishing zebrafish models of both dominant gain of function and recessive loss of function for this gene. Morpholino-based knock down studies lead to significant neuromuscular abnormalities, including poor swimming ability, truncal curvature, and loss of birefringence, all indicative of defective muscle structure and function within the first week of life. Studies to model the dominant variants are in progress.

http://dx.doi.org/10.1016/j.nmd.2018.06.277

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Clinical, genetic and pathological characterization of a wide cohort of UK patients with *NEB* gene related nemaline myopathy

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Recessive *NEB* gene mutations are the most common cause of nemaline myopathy (NM), characterized by early onset generalized weakness and nemaline rods on muscle histopathology. Here we report a clinical, pathological, and genetic evaluation of 46 patients (42 families) with NEB-related NM referred for diagnosis to the Dubowitz Neuromuscular Centre. *NEB* gene analysis was performed by next generation sequencing. Review of available clinical data suggests a typical course in 26/38 patients, with onset at birth/first year of life, hypotonia and/or developmental delay. All 26 achieved independent ambulation and showed prominent axial weakness, 7 with severe foot drop. Scoliosis and/or kyphosis was observed in 13/26 patients. 9/25 needed overnight respiratory support, 10/24 had dysphagia (9 needing a PEG), and 10/20 variable speech involvement. Seven/38 patients showed more severe prenatal/neonatal onset, with early termination of pregnancy in one case and death < 6 months in 2. The remaining patients showed severe skeletal and respiratory weakness. Finally, 5/38 individuals had a later onset (>2 years of age) and followed a milder disease course. 32 patients were homozygous or compound heterozygotes for 2 NEB variants. Phasing of variants is in progress in 14 patients with 2 *NEB* variants. Altogether, we identified 53 variants, 16 frameshift, 10 stop and 10 splice site. Muscle biopsies were available in 16 patients. Frequent nemaline rods (14/16) and slow fibre predominance (9/16) were common findings. In 2 cases no rods were seen on light microscopy. The pathological spectrum also included increased central nuclei (2 cases), frequent cytoplasmic bodies (2 cases), and features of rod-core myopathy (2 cases). Although further deep phenotypic analysis is in progress, the available results confirm the wide clinical and pathological spectrum of *NEB*-related NM and further expand current knowledge on this rare condition.

http://dx.doi.org/10.1016/j.nmd.2018.06.278

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The clinical, genetic, and pathological findings in a Chinese cohort of patients with hereditary nemaline myopathy

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We aimed to identify the causative mutations of hereditary nemaline myopathy and to investigate the clinical, and pathological features in various genotypes. Methods: We recruited 48 patients with hereditary nemaline myopathy who had been diagnosed by muscle biopsies in our neuromuscular pathology lab from 2007 to 2017. Their clinical data and myopathological findings were retrospectively collected and analyzed. Next generation sequencing was used to identify the causative gene mutations in 40 patients. The onset age of these 48 patients ranged from 0 to 60 years old and the disease course ranged from 2 months to 38 years. Clinically, 23, 14 and 11 patients were typical congenital type, childhood or juvenile onset type and adult onset type, respectively. Molecular genetic analysis in 40 patients revealed possible pathogenic variants in 32 patients (80.00%), including 8 known mutation and 42 novel variants. *NEB* gene was the most frequent (23 patients, 57.50%), followed by *ACTA1* (4 patients, 10.00%), *RYR1* (2 patients, 5.00%), *KBTBD13* genes (1 patient, 2.50%), *TNNT1* (1 patient, 2.50%), and *MYO18B* (1 patient, 2.50%). Pathologically, thirteen patients showed coexistence of other myopathological features in addition to the presence of nemaline bodies in the muscle fibers, i.e., minicores in 4, cores in 3, central nuclei in 3 and fiber type disproportion in 3 patients. Nemaline bodies were present subsarcolemmally or in the cytoplasm of muscle fibers in patients with *NEB* mutation. In patients with *ACTA1* mutation, nemaline bodies appeared in cluster or as thin filament in the region of disrupted myofibril. In patients with *RYR1* mutation, there were rod-like structures formed by distorted Z-discs in the region of disrupted myofibrils. Hereditary nemaline myopathy showed wide clinical and genetic spectrum. Myopathological changes also revealed some difference depending on different genotypes. *NEB* is the most frequent causative gene in our patient cohort.

http://dx.doi.org/10.1016/j.nmd.2018.06.279

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Core and rod myopathy due to a novel mutation in BTB domain of *KBTBD13* gene presenting as LGMD

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A 59 years-old man complained about progressive pelvic and scapular girdles weakness since he was 50. Clinical examination revealed a generalized muscle hypertrophy, slowly movements and proximal muscle weakness. CK level ranged from 250 to 600 UI/L. Morphological data from three muscle biopsies were available. Nemaline rods were detected in two of three biopsies. *ACTA1*, *RYR1*, and *NEB* genes were initially ruled out. Because of muscle MRI features and clinical phenotype, mutation on *POGLUT1* was suspected. Alpha-dystroglican showed normal immunostaining on muscle biopsy but reduction on WB. Molecular analysis of *POGLUT1* was negative. Finally, a third biopsy was performed and revealed the presence of cores by optic microscopy whereas small rods were detected by electron microscopy. Type 2 hypotrophy was not observed in any of three muscle biopsies. Sanger sequencing revealed a novel missense mutation in BTB domain of *KBTBD13* gene leading the diagnosis of core and rod myopathy. Mutation falls at the end of the alpha4 helix and seems to affect the self-association of BTB domain but not the BTB-Cul3 interaction. NGS panel for congenital myopathies ruled out other possible genes implicated in core and rod myopathies. Our findings expand clinical and genetical spectrum of core and rod myopathies.

http://dx.doi.org/10.1016/j.nmd.2018.06.280

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Comparison of new mouse models with different variants in the nebulin gene

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Mutations in the nebulin gene (*NEB*) are the most common cause of autosomal recessive nemaline myopathy (NM; ~50% of all NM cases), and a rare cause of distal myopathy (DM). Despite this knowledge, the exact pathogenetic mechanisms by which such mutations lead to muscle phenotypes remain unclear. We have developed murine models with different combinations of *Neb* variants to better elucidate the pathogenetic mechanisms underlying *NEB* skeletal muscle disease. We have characterised three mouse strains with (1) homozygous missense variants, KI*Neb*Y2303H(+/+), within a conserved actin-binding site (genetically similar to patients with DM); (2) heterozygous or homozygous nonsense variants, KI*Neb*Y935X (representative of heterozygous carriers, or of homozygous *NEB*-NM cases, respectively); and (3) compound heterozygous *Neb* variants, KI*Neb*Y2303H(+/-),Y935X(+/-) (matching the genetics of most patients with typical *NEB*-NM). We previously showed that the compound heterozygous mice survive beyond 12 months of age and have striking skeletal muscle pathology, including nemaline bodies and cores. Remarkably, yet as expected, homozygosity for the nonsense variant (KI*Neb*Y935X(+/+)) appears to be lethal in the early postnatal period, if the mice are born. Here, we studied and compared the structure of skeletal muscles of the different *Neb* strains histologically, and evaluated the ultrastructural abnormalities by electron microscopy. Physical performance of the mouse models was assessed by standard *in vivo* phenotypic tests, and whole-muscle and single-fibre physiology were assessed *in vitro*. Additionally, we have investigated the localisation of tropomodulin 4, an actin-binding protein shared by the sarcomere and the sarcoplasmic reticulum. These new mouse models will be useful in elucidating nebulin function, deciphering the pathogenetic mechanisms underlying *NEB*-NM and *NEB*-DM, and evaluating therapeutic approaches, including gene-based therapies.

http://dx.doi.org/10.1016/j.nmd.2018.06.281

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Proteomic profiling in nemaline myopathy to identify disease subclass biomarkers

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Nemaline myopathy (NM) is a muscle disorder that can cause death or lifelong disability. NM is clinically and genetically heterogeneous and is only considered a single disease due to the presence of nemaline rods on muscle biopsy. While diagnostically helpful, the presence of nemaline rods does not correlate with disease severity. When subclassification of NM is attempted based on causative gene, it does not predict patient prognosis well. We have observed considerable variation in disease biology and the impact of anti-myostatin therapy across the *Acta1* H40Y, *Acta1* D286G, and *Neb* cKO mouse models of NM. We hypothesize that as-yet-unappreciated biological processes play a role in the weakness of NM, and that biomarkers related to these processes can be used to relate subsets of NM patients to existing animal models. We have performed proteomic analysis of the Acta1 H40Y model of NM to identify differences in protein expression in comparison

to their wild type counterparts. Based on our findings, we interrogated immunohistochemical biomarkers (including proteins with the highest degree of overexpression in *Acta1* H40Y mice, and those involved with potential mechanisms of weakness) in frozen skeletal muscle samples from *Acta1* H40Y, *Acta1* D286G, and *Neb* cKO mouse models. Interestingly, several of these markers (Tmod1, Coronin 6, Pascin 3) were present in the pathological aggregates of *Acta1* H40Y tissue but not in pathological aggregates in the other two NM models. Evaluation of human NM muscle revealed increased expression of *Tmod1*, *Coronin* 6, *Pascin* 3 in one of six samples analyzed to date. Current work is focused on expanding the analysis of human samples and performing similar proteomics analyses using tissue from *Acta1* D286G, and *Neb* cKO mice at various disease stages. Our work will help correlate biochemical abnormalities to weakness and pathology across NM models and will be used to develop new strategies of biomarker evaluation and disease classification in NM.

http://dx.doi.org/10.1016/j.nmd.2018.06.282

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Recessive congenital fiber type disproportion caused by *TPM3* mutation

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Mutations in *TPM3* gene represent a common cause of congenital fiber type disproportion (CFTD), but can also lead to other phenotypes like nemaline myopathy, cap myopathy, and congenital muscle stiffness. The clinical severity is also highly variable and genotype/phenotype correlations have been inconsistent. The majority of previously reported *TPM3*-associated diseases are dominantly acting, either inherited or *de novo*. Recessive cases are very rare and previously related to severe forms of recessive nemaline myopathy and one severely affected patient with CFTD. Here we present an autosomal recessive CFTD case harboring a novel homozygous mutation in *TPM3* presenting with a mild proximal phenotype. Case Report: a 14-year-old female, only child of consanguineous parents. She was born hypotonic followed by delayed acquisition of motor milestones. Head support was achieved at the age of 6 months and gait at 30 months. At the time of the evaluation, she could walk for more than 1000 meters, climb stairs without support, but could never jump. The physical exam showed facial weakness, mild ptosis but no ophtalmoparesis and mild thoracic deformity. She presented a mild proximal cervical weakness combined with a moderate involvement of cervical flexors and no distal weakness. Muscle biopsy of the biceps brachii performed at the age of 4 years showed fiber type disproportion with type 1 predominance and smallness without other structural features like rods, nuclear centralization or cores. Whole exome sequencing revealed a novel homozygous missense variant (p.R179G) in exon 5 of TPM3 gene. The variant is not present in the population databases (EXAC, GNoMED, EVS), it is located in a very conserved residue and is predicted to be damaging according MetaSVM and MetaLR. Herein we presented a novel homozygous variant in *TPM3* gene causing a mild CFTD expanding the phenotype-genotype correlations related to this gene and also adding a new variant associated with muscle disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.283

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Congenital fiber type disproportion with mutations in tropomyosin 3 (*TPM3*) gene presenting as respiratory failure

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Congenital fiber type disproportion(CFTD) is a rare subtype of congenital myopathy. CFTD is clinically heterogenous and histologically marked by hypotrophy of type I fibers compared with type 2 fibers. CFTD has been related with mutations in *ACTA1, SEPN1, RYR1* and *TPM3* genes. Particularly, TPM3 mutation was identified to the most frequent cause of CFTD and was also detected in cap myopathy and nemaline myopathy. We report autosomal dominant *TPM3* missense mutations with CFTD in a family over two-generations. The two patients, the brother and sister, experienced first symptoms of muscle weakness in infancy with delayed motor milestones and followed a slowly progressive course. They presented generalized muscular hypotrophy, neck flexor muscle and distal limb muscle weakness, elongated face, retrognathia, high arched palate and scoliosis. Respiratory function became critical in two patients despite relatively good limb strength. The brother presented in respiratory arrest during sleep. The sister did not complain of difficulty on walking and climbing stairs but presented in respiratory failure needing ventilator. The finding of electromyography was compatible with myopathy and muscle biopsy showed type 1 fiber atrophy with predominance in the absence of other notable pathological findings such as nemaline rods and cap structures. *TPM3* missense mutation c.502C>T (p.R168C) in exon 5 was identified by a target NGS. We confirmed CFTD caused by TPM3 mutation in this family. CFTD patients with mutation in *TPM3* have been previously reported that many patients required nocturnal noninvasive ventilatory support despite remaining ambulant and several patients of these abruptly presented in respiratory failure. All patients in our family also showed sudden respiratory failure with relatively spared limb weakness. Therefore, it is clinically important for monitoring respiratory function regularly in CFTD patients with *TPM3* mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.284

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Congenital fatal cap-rod myopathy due to a *de novo* autosomal dominant pathogenic *ACTA1* variant

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Cap disease is a rare structural congenital myopathy (CM) associated with hypotonia, proximal and facial muscle weakness, and frequently scoliosis and respiratory involvement. Mutations in *TPM2, TPM3* and *ACTA1* have been associated with cap disease, as well as nemaline myopathy. Combined caps and nemaline rods have been reported in the same patient due to a mutation in *TPM3*. Here, we report the first case of a severe, fatal CM with distinct and separate caps and nemaline rods identified in skeletal muscle biopsies. The patient was born at 37 weeks of gestation, with a history of polyhydramnios, little spontaneous movements at birth, generalised hypotonia, and required immediate ventilatory support. He died 20 days after birth. Ante mortem and post mortem biopsies from the quadriceps, and post mortem biopsies from the biceps and diaphragm showed diffuse fibre hypotrophy without specific structural alterations on light microscopy. Ultrastructural examination of the ante mortem quadriceps biopsy showed several classical cap lesions, and a few of these contained small nemaline rods. The post mortem quadriceps sample showed nemaline rods in several fibres. Both samples showed mitochondrial paracrystalline inclusions in a few interstitial capillary endothelial cells. Ultrastructural findings were key in directing molecular genetic testing. A next generation sequencing panel for 35 congenital myopathy genes identified a *de novo ACTA1* c.739G>C p.(Gly247Arg) variant previously reported in the literature in a patient with severe nemaline myopathy, affecting a highly conserved amino acid, and predicted to affect actin function with In Silico analysis. Our case of *ACTA1*-related cap-rod myopathy is the most severe presentation of a CM with caps or cap-rods described till date. The case further cements the notion of caps and rods being part of the 'nemaline spectrum' and highlights the remarkable heterogeneity of lesions within the same muscle or same group of muscles.

http://dx.doi.org/10.1016/j.nmd.2018.06.285

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The international database of titin gene variations and their phenotypes

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Titin (*TTN*) mutations are the cause of a wide spectrum of hereditary muscular diseases collectively termed titinopathies. Virtually every individual in the general population carries rare *TTN* variants. Not all variants are pathogenic and a more profound understanding of the phenotype-genotype correlations is needed. There is a need to collect all reported, newly detected and rare *TTN* variants from patients worldwide and combine these into a single accessible database, for larger experience and conclusions on genotype-phenotype correlations. At the 219th ENMC (European Neuromuscular Centre) workshop 2016 it was agreed that a *TTN* specific database shared between the research groups was needed. It was decided that genetic and clinical data will be tested on a full-featured genomic analysis RD-Connect platform already available in collaboration with The University of Newcastle and Centro Nacional de Análisis Genómico (CNAG-CRG) Barcelona. A custom clinical form, based on PhenoTips, was drafted for collecting data. The platform was evaluated, and seems to fulfil the expectations. A shared supergroup for titinopathies was created for the registered users with variant calls and phenotypic description permitting access by other researchers who have joined the group. RD-Connect allows the supergroup users to access the phenotypic and NGS data uploaded by group members, and also provides access to datasets uploaded by the hundreds of other users of the platform. These may be cases (both neuromuscular and other unrelated rare diseases) in which *TTN* mutations are not implicated, thus providing a large control cohort (currently over 3000 cases but increasing to over 20,000 cases in the next 2 years) enabling the consortium to explore the range of benign variation in *TTN*. Other groups in the consortium have also started uploading their data into the database. The goal is to optimize its functionality and increased data content.

http://dx.doi.org/10.1016/j.nmd.2018.06.286

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Congenital titinopathy: severe and atypical presentations

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Congenital titinopathy is a prenatal/infant-onset genetic muscle disorder caused by recessive *TTN* mutations. The true prevalence of of this disorder remains unknown, however the number of confirmed cases is climbing exponentially. We have identified four informative congenital titinopathy cases with convincingly pathogenic *TTN* mutations in *trans*. These cases extend our understanding of the spectrum of weakness and additional clinical features that can be associated with this emerging titinopathy. The first three cases are severely affected infants. All had a history of reduced fetal movements and were born at term with profound hypotonia and no respiratory effort. All required immediate resuscitation and intubation. One had congenital fractures, two had congenital quadrimelic joint contractures, two had atrial or ventricular septal cardiac defects, and two had intracerebral abnormalities likely secondary to birth trauma. Two died shortly after withdrawal of care on day one of life & three months of age respectively. The third remains reliant on full time ventilatory support (age 9 months). The fourth case is a 21-year-old female who was born with several congenital-titinopathy-like features including congenital contractures (camptodactyly, unilateral talipes), a cardiac abnormality (peripheral pulmonary stenosis), ptosis (congenital), and a high arched palate. However, this patient was not clinically weak at birth and has remained strong over time. She also has a range of striking additional features including Noonan-like facies, a low posterior hairline, neck webbing, short stature and bilateral axillary pterygia. She has no pathogenic-looking variants within established Noonan syndrome/syndrome-like genes. In view of the features present in these patients, we recommend that congenital titinopathy be considered in all weak infants with features suggestive of a primary muscle disorder and in patients with Noonan-like or multiple-pterygia-contracture phenotypes.

http://dx.doi.org/10.1016/j.nmd.2018.06.287

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Distal upper limb onset myopathy in the first Chilean case reported with titinopathy

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The titin gene (*TTN*, OMIM188840) in 2q31.2, comprises 364 exons and codifies for the giant muscle protein titin. Mutations in *TTN* cause of at least eleven different phenotypes including LGMD2J, CMD1G cardiomyopathy, dilated 1G (AD), EOMFL congenital myopathy with fatal cardiomyopathy (AR), HMERF (AD), TMD tibial muscular dystrophy (AD), CMH9 cardiomyopathy, familial, hypertrophic 9 (AD), centronuclear myopathy related to *TTN* (AR). Up to date no patients with titinopathy have been identified in Chile. We describe the case of a 30-year-old man presenting with asymmetric extensor finger weakness in the upper limbs at onset, followed by selective deltoid involvement, with relative sparing of leg muscles. MR imaging revealed selective finger extensors and deltoid involvement in upper limbs, in addition to semitendinosus and peroneal muscles in the thighs and legs respectively. No respiratory or cardiac involvement was observed. Deltoid muscle biopsy showed severe dystrophic changes, rimmed vacuoles and protein aggregates with desmin, titin and myotilin labelling on immunohistochemistry. CK levels were slightly increased. There were no other affected relatives. A NGS panel for 115 genes related to congenital and progressive muscle dystrophies, and congenital myasthenic syndromes performed with MiSeq (Illumina) revealed two missense mutations on *TTN*: c.54710T>C, (p.Leu18237Pro) on exon 282; and c.95372G>A, (p.Gly31791Asp) on exon 343, both mutations and their in trans segregation in the family were confirmed by Sanger sequencing. The patient's onset phenotype does not correspond entirely with none of the described forms of titinopathy. The mutation c.95372G>A was reported associated to AD-HMERF in a family of European origin; but the mutation c.54710T>C, also affecting the A-band of titin, has uncertain pathogenic significance (VUS). Our case adds yet another presenting phenotype titinopathy: adult onset, recessive upper limb, distal titinopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.288

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Loss of sarcomeric scaffolding as a common baseline histopathologic lesion in titin-related myopathies

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Titin-related myopathies are extremely heterogeneous clinical conditions associated with mutations in the *TTN* gene. To define histopathologic boundaries of *TTN*-related myopathies and possibly overcome the difficulty in assessing the pathogenic role of *TTN* variants, we performed a thorough morphological skeletal muscle analysis including light and electron microscopy in 23 patients presenting pathogenic autosomal dominant (AD) or autosomal recessive (AR) mutations located in different titin domains. Patients presented either an AR congenital myopathy (AR-CM) (n= 10), an AR early-onset Emery-Dreifuss-like myopathy (AR-ED) (n= 4), an AR adult-onset distal myopathy (AR-DM) (n= 4), or a Hereditary Myopathy with Early Respiratory Failure (HMERF) (n= 5). By light microscopy, we identified a consistent histopathologic pattern in AR-CM patients characterized by oxidative staining defects spanning from mild intermyofibrillar irregularities to multifocal cores with prominent nuclear internalization. This pattern was confirmed by ultrastructural studies that demonstrated the presence of multiple narrow core lesions and/or well-delimited areas of myofilament loss affecting one or a few sarcomeres. These distinctive regions showed M-line dissolution by subsequent disintegration of thick filaments. Z-line alterations resembling small "pennants" were present. AR-ED and AR-DM groups showed inconstant presence of rimmed vacuoles and/or other protein inclusions, associated with variable degree of restricted myofibrillar changes as M-line dissolution with almost intact Z-line, or small and focal "pennant" lesions affecting a single sarcomere. In HMERF group we confirmed the presence of cytoplasmic bodies as the main histopathological lesion with subtle ultrastructural disorganizations. As a whole, we have established the heterogeneous morphological spectrum of *TTN*-related myopathies and identified characteristic M-line disruption with some loss of thick filaments as a common and recognizable pattern of structural alterations that could point toward considering the pathogenicity of *TTN* mutations.

http://dx.doi.org/10.1016/j.nmd.2018.06.289

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Neonatal presentations of recessive *TTN*-related myopathy: an emerging distinct clinical phenotype

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With the increasing availability of next generation-based sequencing, the phenotypic spectrum associated with *TTN*-related myopathies is ever-expanding. Early clinical recognition is essential to facilitate accurate genetic testing methodologies, to aid in pathogenicity interpretation of the large number of *TTN* variants identified, and to direct proper medical care and management. Here we report four unrelated patients, aged 2 to 12 years, with genetically confirmed biallelic *TTN* mutations who display a consistent, recurrent phenotype that is recognizable at birth. Retrospective review of the neonatal presentations of these four patients revealed characteristic clinical features, the most prominent of which is striking positioning of the hands and feet, namely bilateral wrist extension with ulnar deviation of the hands and extreme ankle dorsiflexion of the feet with associated Achilles tendon hyperlaxity. Additional salient features include reduced fetal movements and oligohydramnios, along with bulbar weakness clinically manifesting as dysphagia and feeding difficulties, generalized hypotonia and joint hypermobility. Bilateral hip dysplasia and respiratory distress or apnea was also seen in three out of four neonates. This cohort delineates a distinct and recognizable neonatal clinical phenotype associated with recessive *TTN*-related myopathy and may aid in the recognition of titinopathy in neonates presenting with features of a congenital myopathy. It can be added as a "titin-compatible" phenotype that will also help in interpreting *TTN* genotypes "of uncertain significance." Additional neonatal titinopathy cases will surely expand on this phenotype. Longitudinal data are needed to further characterize this phenotype and increase our understanding of the natural history of titinopathy as well as expand genotype-phenotype correlations.

http://dx.doi.org/10.1016/j.nmd.2018.06.290

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Taking on the titin: semitendinosus muscle involvement as a diagnostic marker of early onset recessive *TTN*-related myopathy

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The titin (*TTN*) gene encodes the largest known human protein and is expressed primarily in cardiac and skeletal muscle. Titin has become accessible to testing due to next generation sequencing, expanding the phenotypic spectrum of *TTN*-related myopathies. A major challenge that has emerged with routine sequencing of such a large gene is the interpretation of pathogenicity of numerous *TTN* variants. In the absence of a uniform phenotype, additional diagnostic tools, such as muscle imaging, are needed to aid clinicians in assigning a diagnosis of *TTN*-related myopathy. To that purpose, muscle MRI was obtained in 11 patients with presumed recessive *TTN*-related myopathy. Non-contrast axial T1 images of the proximal thigh, distal thigh, and lower leg muscles were scored in a blinded fashion using a 5-point scale, based on T1 signal intensity. In the thigh, the hamstrings received a higher combined score compared to the quadriceps, which was quite variable. Within this muscle group, in nine of 11 patients, there was selectively more severe involvement of the proximal semitendinosus compared to semimembranosus and biceps femoris. In the lower leg, the soleus had the greatest signal increase across patients. The peroneal group showed a greater signal increase compared to the other anterior compartment muscles, particularly compared to the extensor digitorum longus, which was relatively spared. Involvement of other muscles was more variable, notably the tibialis anterior. This series highlights a mostly consistent pattern of selective semitendinosus involvement on MRI in early onset recessive *TTN*-related myopathy, similar to observations seen in dominant *TTN*-related myopathy, while tibialis anterior involvement, typical in dominant *TTN* disorders was inconsistent in the recessive cohort. This pattern, when present, can be added to the "deep phenotype" of patients with *TTN* variants, aiding specifically in cases with inconclusive genotypes.

http://dx.doi.org/10.1016/j.nmd.2018.06.291

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A ddPCR method for the analysis of copy number variation in the segmental duplication regions of the sarcomeric giants nebulin and titin

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The sarcomeric giants nebulin and titin (encoded by the *NEB* and *TTN* genes, respectively) both harbour large segmental duplication (SD) regions known to be expressed. In *NEB*, this region contains eight exons repeated three times. In *TTN*, nine exons are repeated threefold, after which the two first exons of the block reappear alone a fourth time. Mutations in *NEB* are known to cause nemaline myopathy (NM), and mutations in *TTN* can cause different myopathies, including tibial myopathy and cardiomyopathies. Using our targeted NM Comparative Genomic Hybridization array (NM-CGH-array), we have previously shown that copy number variations (CNV) in the *NEB* SD are potentially pathogenic. Recent studies using our CGH-array for neuromuscular disorders (NMD-CGH-array) revealed recurrent and potentially pathogenic CNVs in the *TTN* SD region also. To validate these findings, we have established a custom Digital Droplet PCR (ddPCR) assay for the analysis of the SD regions of *NEB* and *TTN*.

We have created custom assays for exons 4 and 8 of the *NEB* SD, and for exons 1-2 and exons 7-8 of the *TTN* SD. This allows us to determine the copy number difference between the sections of the *TTN* SD that are repeated three versus four times. The ddPCR method was validated using four positive and seven negative controls that had been run on the NMD-CGH-array.

Hitherto, we have been able to determine the copy number in both control and patient samples using our method. Our studies show that CNVs in the *TTN* SD are recurrent and appear in roughly 25% of both healthy and affected individuals.

Our ddPCR assay for the SD regions of *NEB* and *TTN* constitutes a rapid, specific and inexpensive method for the analysis of CNVs within these regions. The potential pathogenicity of CNVs in the SD region of *TTN* SD is currently under assessment.

http://dx.doi.org/10.1016/j.nmd.2018.06.292

MYOFIBRILLAR AND DISTAL MYOPATHIES

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Assessment of new lectin-based protocols for the diagnosis of GNE myopathies

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GNE myopathy is an autosomal recessive disorder characterized by distal muscle weakness as well as the relative sparing of quadriceps muscle. The affected gene, *GNE*, encodes a bifunctional enzyme that catalyzes the first steps in the biosynthetic pathway of 5-N-acetylneuraminic acid (Neu5Ac or sialic acid). A diagnosis of GNE myopathy is based on a combination of clinical and pathological evidence and confirmed by genetic test. Features observed in a muscle biopsy are non-specific and include variation in fiber size, rimmed vacuoles and protein aggregates. There is currently no robust histological test for GNE myopathy, although lectin staining of affected muscles has been studied in order to identify decreased sialylation of glycoproteins associated with this pathology. We sought to implement lectin staining of muscle biopsies as a diagnostic biomarker for defective GNE and as a tool to assess the efficacy of clinical trials. A panel of lectins was tested on muscle biopsy samples from controls and patients affected by GNE myopathy and well as other types of muscular dystrophy. Blind scoring demonstrated that, although some samples exhibited variable intensity of staining across the tissue section, GNE samples could be easily differentiated from normal skeletal muscle. However, the presence of endomysial fibrosis in disease controls led to variability in lectin labelling with the risk of false-positive results. Here we present a new promising lectin-based procedure developed to overcome the problem of misdiagnosing GNE myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.293

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GNE myopathy in Chinese population: hotspot and novel mutations

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GNE myopathy is a rare autosomal recessive distal myopathy caused by bi-allelic mutations in *GNE* gene. In this study, we summarized the clinical features, pathological characteristics, and genetic profiles of 46 GNE patients. The clinical and mutational profile of 54 previously reported Chinese patients were also reviewed. A total of 21 novel mutations, including a gross deletion spanning exon 1-2 and a retrotransposon insertion were found in our cohort, enlarging the spectrum of *GNE* mutations. The most frequent mutation in Chinese population was p.D207V, which accounts for 25.5% of total alleles (51/200). The age of onset was much later in the patients carrying p.D207V compared to other patients, indicated the less deleterious effect of p.D207V on enzyme activity. GNE myopathy may be overlooked in China with a relatively milder phenotype due to a less deleterious common mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.294

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Clinical and genetic profiles of GNE myopathy in Korean patients

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GNE myopathy is caused by recessive *GNE* mutations and generally known as a muscle disease characterized by initial presentation of foot drop, the presence of rimmed vacuoles in muscle pathology and rare occurrence of cardiac and respiratory difficulties. Our study presents genetic profiles and characteristic patterns of disease progression and severity in 44 Korean patients with GNE myopathy. A missense mutation p.Val603Leu was the most common followed by p.Cys44Ser. Most of the mutations were shared by Japanese and Chinese patients. Foot drop was the presenting symptom in 43% of patients, while 29% reported proximal leg weakness as the first symptom and 14% their calf weakness. The number of functional joints tended to remain stable for the first 10 years, then decreased over the next 10 years. The wrist joints were the last to lose functional movement whether the weakness started from ankle or hip. Disease progression was more rapid in the patients with limb-girdle phenotype, and in the patients with their mutations in kinase domain. This data will provide a guidance in the clinical management of GNE myopathy, and also a perspective in designing clinical trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.295

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A novel exon 1 deletion mutation in the *GNE* gene in a GNE myopathy patient

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GNE myopathy caused by the UDP-N-acetyl-glucosamine 2-epimerase/N-acetylmannosamine (*GNE*) gene is characterized by muscle weakness and atrophy of lower muscles with sparing the quadriceps. We describe a 32-year-old woman who suffered GNE myopathy, with symptoms presenting in distant muscles of lower limbs and spreading to her legs. The patient's serum level of creatine kinase was mildly increased. Mild myogenic changes in tibialis muscles in muscle electromyographic and moderate fatty infiltration in magnetic resonance imaging were detected. Histopathological examination revealed variation in muscle fiber size, rimmed vacuoles and disorganized intermyofibrillar networks. DNA sequencing analysis detected novel com-

pound heterozygous mutations c.620A>T (exon 4) and exon 1 deletion. We reported a GNE myopathy patient with novel compound heterozygous *GNE* gene mutations and expanded the genotypic spectrum of GNE myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.296

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A novel mutation in *MYH7* giving rise to different phenotypes in a mother and her daughter

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Early signs of skeletal muscle involvement may alert clinicians in identifying mutations in genes that might cause serious involvement of either cardiac or skeletal muscles. Typical examples of such genes are *LMNA*, *DMD* and *MYH7*. Mutations in *MYH7* may cause several different types of myopathy including cardiomyopathy and Laing early-onset distal myopathy. However, the phenotype even within the same family may differ. A 14 year old girl had experienced episodes of tachycardia. Her parents had registered reduced physical endurance over several months and that she could become cyanotic on her lips. She was diagnosed with a severe dilated cardiomyopathy. At the time of diagnosis, it was difficult to distinguish between symptoms related to her cardiomyopathy and possible skeletal muscle involvement. Skeletal muscle biopsy revealed "fiber type disproportion" and 6 years after her diagnosis of cardiomyopathy she has clear involvement especially of axial muscles. Her mother had also previously been diagnosed with cardiomyopathy during a pregnancy but this had almost subsided on medical treatment. The mother had always been clumsy walking and had experienced increased symptoms from skeletal muscles. At the age of 51 years she also has prominent axial weakness in addition to typical features of Laing distal myopathy. Genetic testing revealed a novel mutation in *MYH7* in both mother and daughter that probably is the cause of this dominant condition. This mutation has also been found in a younger daughter – so far with no cardiac symptoms. We describe a novel mutation in the *MYH7* gene that has given rise to severe cardiomyopathy in a young girl. Earlier diagnosis of her mother's muscle disease might have led to a more favorable prognosis of this girls serious cardiac disorder.

http://dx.doi.org/10.1016/j.nmd.2018.06.297

P.250

The clinical, myopathological characteristics of a Chinese cohort of myofibrillar myopathy: a retrospective study

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Myofibrillar myopathy is a group of hereditary myopathies characterized by myofibrillar dissolution and abnormal intramuscular accumulation of proteins. Here we present 14 Chinese patients with pathologically diagnosed myofibrillar myopathy. Our patients show a male predominance (2.5:1), and the age of onset ranges from childhood to senior (5yr to 67yr) with a median age of 41yr. On physical evaluation, 57.1% patients demonstrate a mixed proximal and distal weakness, 28.6% a predominantly proximal involvement and 14.3% distal. Other common clinical features include joint contracture (35.8%), respiratory insufficiency (28.6%) and paresthesia/hypesthesia (28.6%). Of the 13 patients who underwent electrophysiological evaluation, all show myopathic changes and 78.6% have variable neurogenic changes, the majority of which is consistent with an axonal polyneuropathy with a preferential motor nerve involvement. Next generation sequencing was performed on 13 patients, and 12 were identified to harbor pathogenic mutations in genes including *DES, BAG3, FLNC, FHL1* and *TTN*. Four novel mutations were found in *DES, FLNC* and *FHL1*. On muscle pathology, eosinophilic bodies were present in all patients with mutations in *DES, BAG3, FHL1* and *TTN*, but not in the two cases with *FLNC* mutations. In contrast, patients associated with *FLNC* tend to demonstrate more rimmed vacuoles than others. The patients with the most rubbed-out fibers were the ones with *DES* mutations, while those with *FLNC* mutations did not show any. Abnormal accumulation of desmin was present in all patients, except the ones with *FLNC*, to a variable extent. It seems that patients with *FLNC* have a distinctive myopathological picture, ie. the presence of more rimmed vacuoles without eosinophilic bodies. These, together with the absence of abnormal desmin accumulation, make it tantalizing to propose that the patients with *FLNC* mutations do not share a common etiology with other myofibrillar myopathy cases.

http://dx.doi.org/10.1016/j.nmd.2018.06.298

P.251

Family with a new mutation in the *DES* gene of autosomal recessive transmission

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The desminopathies manifest with different types of characteristics, ages of presentation and even with types of inheritance. The reason for this presentation is a family with a description that presents a phenotype and genotype not described. A 14-year-old patient who visited the clinic due to myalgia, exercise intolerance and serum creatine kinase (CK) levels maintained at around 1000 IU/L; the middle sister has the same symptomatology and the older brother is healthy, the great-grandmothers are sister cousins. A non-invasive hyperCKemia protocol is applied, including DBS Pompe and MLPA *DYS* that are normal. MRI presents a pattern of local involvement (soleus, gastronemius and semitendinosus (grade 1) and paravertebral (grade 2). Muscle biopsy presents a dystrophic profile with vacuoles. In successive years it presents mild palpebral ptosis and minimal facial, scapular and axial weakness (4-). A NGS genetic study with 40 detects a variant in homozygosis not described (c.1372-1G>A) in the *DES* gene. The variant segregates with a recessive pattern in the family study. Myofibrillar protein markers are abnormal, highlighting Desmin accumulations. Currently the brothers have similar manifestations at 22 and 28 years of age. We describe a new pathological variant in the *DES* gene (c.1372-1G>A) with AR transmission causing a desminopathy that presents as paucisintomatic HCK and without cardiac alterations.

http://dx.doi.org/10.1016/j.nmd.2018.06.299

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A case report: a heterozygous deletion (2791_2805 del) in exon 18 of the *FLNC* gene causing filamin C-related myofibrillar myopathies

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Filamin C-related myofibrillar myopathies (MFM) are progressive skeletal myopathies with an autosomal dominant inheritance pattern. The conditions are caused by mutations of the filamin C gene (*FLNC*) located in the chromosome 7q32-q35 region. Genetic variations in the *FLNC* gene result in various clinical phenotypes. We describe a 43-year-old woman who suffered filamin C-related MFM, with symptoms first presenting in the proximal muscles of the lower limbs and eventually spreading to the upper limbs and distal muscles. The patient's serum level of creatine kinase was mildly increased. Mildy myopathic changes in the electromyographic exam and moderate lipomatous alterations in lower limb MRI were found. Histopathological examination revealed increased muscle fiber size variability, disturbances in oxidative enzyme activity, and the presence of abnormal protein aggregates and vacuoles in some muscle fibers. Ultrastructural analysis showed inclusions composed of thin filaments and interspersed granular densities. DNA sequencing analysis detected a novel 15-nucleotide deletion (c.2791_2805del, p.931_935del) in the *FLNC* gene. The patient's father, sister, brother, three paternal aunts, one paternal uncle, and the uncle's son also had slowly progressive muscle weakness, and thus, we detected an autosomal dominant inheritance pattern of

the disorder. A novel heterogeneous 15-nucleotide deletion (c.2791_2805del, p.931_935del) in the Ig-like domain 7 of the *FLNC* gene was found to cause filamin C-related MFM. This deletion in the *FLNC* gene causes protein aggregation, abnormalities in muscle structure, and impairment in muscle fiber function, which lead to muscle weakness.

http://dx.doi.org/10.1016/j.nmd.2018.06.300

P.253

Severe intestinal pseudo-obstruction in a p.R405W desmin knock-in model: a new phenotype lead to light smooth muscle involvement in myofibrillar myopathies

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The intermediate filament desmin, specifically expressed in striated and smooth muscle cells, forms a filament network which provides maintenance of cellular integrity, resistance to mechanical stress, force transmission and mechanochemical signaling. Abnormal expression or lack of desmin leads to a progressive disruption of the contractile machinery, which can be observed in the muscles from patients affected by myofibrillar myopathies (MFM) due to mutations of the desmin gene *DES* (*DES*-MFM). To clarify the pathophysiology of *DES*-MFM, we generated a mouse KI model expressing the R405W *DES* mutation, homologous to human R406W. This mutation is associated with a severe and relatively early clinical phenotype in patients, which develop muscular weakness, cardiopathy and respiratory failure from the third decade of life. Molecular studies showed that p.Arg406Trp desmin has a reduced ability to support longitudinal annealing as well as radial compaction, two essential steps required for the formation of the desmin network. Heterogygous $Des^{WT/R405W}$ as well as homozygous $Des^{R405W/R405W}$ KI mice showed abnormal accumulation of desmin at the subsarcolemmal membrane in striated muscles. Homozygous animals died early (at 3.4 ± 1.2 months) and developed severe dilatation of the intestinal tract associated with food stasis in the lumen around 3 months. Echographic and histological studies showed a thickening of the colon and desmin aggregates in all muscle segments of the digestive tract. Functional studies revealed reduced spontaneous contraction and strength generation of the homozygous duodenum, suggesting an alteration of the mechanical properties of smooth muscle cells. Intestinal malapsorption and pseudo-obstruction have been reported in very rare *DES*-MFM patients. Our model brings to light the importance of desmin for intestinal smooth muscles, and suggests that smooth muscle involvement may have been underestimated in patients suffering from MFMs.

http://dx.doi.org/10.1016/j.nmd.2018.06.301

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Pyroxd1 mutations cause recessive adult-onset slowly progressive LGMD

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Limb-girdle muscular dystrophy (LGMD) is a group of inherited muscle diseases with slowly progressive, predominantly proximal myopathy. The phenotype of LGMD ranges from mild late-onset to severe early-onset disease. At least 31 different genes have been implicated in LGMD. Mutations in *PYROXD1* gene was recently reported to cause recessive muscle disease. The described phenotype of *PYROXD1* disease was congenital myofibrillar myopathy with symptom onset between infancy and 8 years. Internalized nuclei and myofibrillar disorganization were described as specific histopathologic features. We report on four Finnish patients, of whom two are siblings, with homozygous or compound heterozygous variants in *PYROXD1* underlying adult-onset LGMD. Three of our patients were homozygous for the previously described variant p.Asn155Ser, and presented with muscle weakness in their teens or early thirties but have remained ambulant to over 60 years of age. Our fourth patient was compound heterozygous for the p.Asn155Ser variant and a previously unknown variant p.Tyr354Cys. He had the onset of proximal muscle weakness as late as aged 49 years. Thus the disease onset in our patients, particularly in the compound heterozygous patient, was considerably later than in the previously reported individuals with *PYROXD1* mutations. Muscle biopsies showed dystrophic changes, excess of fat and fibrosis, necrosis and atrophy but no clear myofibrillar aggregates that would be consistent with myofibrillar myopathy. On muscle MRI the most severe fatty degenerative change was seen in gluteal region and anterior compartment of the thigh with relative sparing of rectus femoris. Our results show that p.Asn155Ser is a common pathogenic *PYROXD1* variant, leading to myopathy with highly variable ages of disease onset. These findings extend the phenotypes caused by *PYROXD1* mutations to adult-onset LGMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.302

SMA THERAPIES II AND BIOMARKERS

P.255

SUNFISH Part 1: RG7916 treatment results in a sustained increase of SMN protein levels and the first clinical efficacy results in patients with type 2 or 3 SMA

E. Mercuri [1], G. Baranello [2], J. Kirschner [3], L. Servais [4], N. Goemans [5], M. Carmela Pera [1], J. Buchbjerg [6], G. Armstrong [7], H. Kletzl [6], M. Gerber [6], C. Czech [6], Y. Cleary [6], K. Gorni [6], O. Khwaja [6]

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy, due to reduced levels of survival of motor neuron (SMN) protein from loss of function of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces only low levels of functional SMN protein. RG7916 (RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA, resulting in an increase of SMN protein. SUNFISH (NCT02908685) is an ongoing multicenter, double-blind, placebo-controlled, seamless study of RG7916 (randomized 2:1, RG7916:placebo) in patients aged 2-25 years with Type 2 or 3 SMA. Part 1 (n=51) is principally assessing safety, tolerability, pharmacokinetics and pharmacodynamics of different RG7916 dose levels. Pivotal Part 2 (n=168) assesses safety and efficacy of the RG7916 dose level selected based on the results from Part 1. An interim analysis of SUNFISH Part 1 showed that RG7916 resulted in a dose-dependent increase in SMN protein levels in whole blood up to a median of 2.5-fold. To date, adverse events have been mostly mild, resolved despite ongoing treatment and were reflective of the underlying disease. There have been no drug-related safety findings leading to withdrawal. Effects on exploratory clinical outcome measures, biomarker results, and a recent update of safety data from SUNFISH Part 1 patients will be presented. Based on the differences in SMN protein levels between SMA severity types, an up to 2.5-fold increase in SMN protein is expected to lead to clinical efficacy. The clinical benefit of RG7916 is being assessed in SUNFISH Part 2, which is ongoing.

http://dx.doi.org/10.1016/j.nmd.2018.06.303

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A study of RG7916 in infants with pre-symptomatic spinal muscular atrophy

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy, caused by reduced levels of survival of motor neuron (SMN) protein from a loss of function of the *SMN1* gene. While SMN1 produces full-length SMN protein, a second gene, *SMN2*, produces only low levels of functional SMN protein. RG7916 (RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA, resulting in an increase of SMN protein. Most motor neuron degeneration occurs in the first months of life in SMA type 1 infants, thus the timing of therapeutic intervention is crucial. Recent studies in pre-symptomatic SMA type 1 infants have shown a higher and more rapid achievement of motor milestones and reduced disease severity when SMN upregulation therapy was administered early. We have designed BN40703 as an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics and pharmacodynamics of RG7916 in asymptomatic infants, aged from birth to 6 weeks of age (at first dose) with genetically diagnosed SMA. Infants with 2-4 *SMN2* copies will be enrolled in the study. All infants will receive RG7916 for 24 months, followed by a 3-year extension phase. Primary analysis will be conducted once the last patient with two *SMN2* copies enrolled has reached 12 months of treatment. The primary endpoint is the proportion of infants sitting without support after 12 months of treatment. Secondary endpoints will include long-term evaluation (2-5 years) of motor milestone achievements and other developmental milestones. BN40703 will provide valuable information about the early administration of RG7916 alongside the ongoing FIREFISH (type 1, NCT02913482), SUNFISH (type 2/3, NCT02908685) and JEWELFISH (type 2/3 previously treated with other *SMN2*-splicing therapies, NCT03032172) studies.

http://dx.doi.org/10.1016/j.nmd.2018.06.304

P.257

JEWELFISH: RG7916 increases SMN protein in patients with SMA that have previously received therapies targeting *SMN2* splicing

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy due to reduced levels of survival of motor neuron (SMN) protein from loss of function of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces only low levels of functional SMN protein. RG7916 (RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA, resulting in an increase of SMN protein. JEWELFISH (NCT03032172) is a multicenter, open-label, exploratory study evaluating the safety, tolerability and pharmacokinetics of daily oral RG7916 in patients with SMA type 2 or 3, aged 12-60 years, who previously participated in a study with therapies targeting SMN2 splicing. The pharmacodynamic (PD) effects on SMN2 mRNA and SMN protein are also being assessed. The study will soon be expanded to include patients >6 months of age with all SMA Types. At abstract submission, 11 patients in JEWELFISH with type 2 or 3 SMA have received RG7916 for a minimum of 3 weeks, and up to 13 months. To date, no drug-related adverse events leading to withdrawal have been reported. Preliminary PD data in whole blood from 10 patients receiving RG7916 showed an up to 4-fold SMN protein increase versus baseline after 4 weeks of treatment. While the patient number in JEWELFISH is limited, the magnitude of the SMN protein increase and the safety observations thus far are comparable to what has also been observed in the SUNFISH Part 1 study (NCT02908685) in type 2 and 3 patients who have not previously received an *SMN2*-targeting therapy. A JEWELFISH update, including safety and PD data, will be presented. The JEWELFISH study is currently recruiting in sites in Europe and the US.

http://dx.doi.org/10.1016/j.nmd.2018.06.305

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FIREFISH Part 1: early clinical results following a significant increase of SMN protein in SMA type 1 babies treated with RG7916

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy, due to reduced levels of survival of motor neuron (SMN) protein from loss of function of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces only low levels of functional SMN protein. RG7916 (RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA, resulting in an increase of SMN protein. FIREFISH (NCT02913482) is an ongoing, multicenter, open-label, two part, seamless study of RG7916 in babies aged 1-7 months with type 1 SMA and two *SMN2* gene copies. Part 1 is exploratory and is principally assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of different RG7916 dose levels (enrollment complete). Confirmatory Part 2 (n=40) assesses safety and efficacy of RG7916, with a primary endpoint of the proportion of babies sitting without support for 5 seconds after 12 months. In an interim analysis of FIREFISH Part 1, a dose-dependent increase in SMN protein levels in whole blood was observed, with an up to 6.5-fold increase vs. baseline after 4 weeks of treatment at the highest dose of RG7916 (range 2.0-6.5-fold). To date, no protocol-defined safety-related stopping rules have been met, and none of the following events have been reported: loss of ability to swallow, tracheostomy or permanent ventilation. Part 1 motor milestone, safety, and survival data for all babies that have been treated for a minimum of 6 months will be presented. The up to 6.5-fold increase in SMN protein observed in FIREFISH Part 1 is expected to lead to clinical efficacy based on the differences in SMN protein levels between SMA severity types (e.g., type 2 *vs*. type 1 with differences of ~2-fold). All doses explored so far have been well tolerated. Part 2 of the FIREFISH study is ongoing.

http://dx.doi.org/10.1016/j.nmd.2018.06.306

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SMN protein levels before and after treatment with RG7916 in type 1, 2 and 3 SMA patients compared to healthy subjects

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Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy, due to reduced levels of survival of motor neuron (SMN) protein from loss of function of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces only low levels of functional SMN protein. RG7916 (RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing towards the production of full-length SMN2 mRNA, resulting in an increase of SMN protein. Studies with RG7916 are currently ongoing in type 1 SMA patients (FIREFISH - NCT02913482) and type 2 and 3 SMA patients (SUNFISH - NCT02908685; JEWELFISH - NCT03032172). At the time of abstract submission, SMN protein data are available from 61 type 2 and 3 SMA patients and from 16 type 1 SMA patients, at baseline prior to treatment and after treatment with RG7916. SMN protein levels in 49 healthy subjects have been collected in two other studies. This data set enables, for the first time, a detailed comparison of SMN protein levels across SMA types and versus healthy individuals, between copy numbers, across a wide age range (3.5 months to 52 years in SMA patients), and in longitudinal data over time for patients on treatment with RG7916 versus patients on placebo. All SMN protein samples have been collected under the same procedures and were analyzed with the same assay, which enables a robust comparison. In SUNFISH and JEWELFISH, SMN protein increased in a dose-dependent manner upon treatment with RG7916, with a median 2.5-fold increase (range 1.5 - 3.5) at the highest dose. In FIREFISH, at the highest dose an individual SMN protein increase of up to 6.5-fold (range 2.0 - 6.5) was observed. This increase in SMN protein is expected to lead to significant clinical benefit, based on the comparison of SMN protein levels in different SMA severity types and healthy subjects.

http://dx.doi.org/10.1016/j.nmd.2018.06.307

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A long-term, open-label, follow-up study of olesoxime in patients with type 2 or non-ambulatory type 3 SMA who participated in a placebo-controlled phase 2 trial

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Olesoxime is an oral, daily administered compound that supports the function of mitochondria. In a previous randomized, double-blind, phase 2 study (NCT01302600) in patients aged 3-25 years with type 2 or non-ambulatory type 3 spinal muscular atrophy (SMA), olesoxime maintained motor function over 24 months, whilst the placebo group declined. OLEOS (NCT02628743) is an open-label extension of the phase 2 study assessing the long-term safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 SMA. One hundred and twenty-nine patients with Type 2 or non-ambulatory Type 3 SMA from the previous Phase 2 study were enrolled and treated with olesoxime (10 mg/kg). The majority have been followed for 12 months (n=104). The primary endpoint is safety and secondary endpoints include change in Motor Function Measure (MFM) Dimension 1 (D1)+Dimension 2 (D2) from baseline to 5 years. The OLEOS baseline visit occurred 2.4-5.1 years after study drug discontinuation in phase 2. Consistent with previous studies, olesoxime was generally safe and well tolerated at the dose assessed. Maintenance of motor function observed over 2 years in the Phase 2 study was followed by a substantial decline in MFM D1+D2 (>2 points/year) after drug discontinuation. However, the ~2-point MFM treatment difference between olesoxime and placebo at the end of phase 2 was maintained at OLEOS baseline. Olesoxime open-label treatment stabilized motor function up to 12 months (mean change in MFM D1+D2 from baseline: 6 months, -0.03 [n=124]; 12 months, -0.22 [n=104]). From 12-18 months, motor function appears to decline gradually, with large variability observed. A study update, including novel 18-month data, will be presented. These data suggest that olesoxime offers the potential to provide meaningful clinical benefit to patients with SMA by preventing loss of motor function, and may play a role in the future therapeutic management of SMA.

http://dx.doi.org/10.1016/j.nmd.2018.06.308

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Safety and efficacy of the oral splice modulator branaplam in type 1 spinal muscular atrophy

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Branaplam is an orally bioavailable molecule that interacts with SMN2 RNA to increase functional survival motor neuron protein and is being developed for treatment of SMA. This open-label, multi-part, first-in-human study is evaluating the safety and efficacy of branaplam in patients with SMA type I. The study enrolled 14 patients, 1 failed screening, and 13 received once-weekly branaplam with planned dose escalation based on safety results. All patients continued from an initial 13-week treatment period into a long-term extension. Five patients died during the trial from disease progression as assessed by the investigators and the independent Data Monitoring Committee. Eight have continued on branaplam for between 28-33 months, with patient ages ranging from 30.5 to 37 months. No maximum tolerated dose for branaplam was reached and adverse events were mostly mild, reversible, and manageable. Branaplam dosing was temporarily reduced due to preclinical toxicology findings in dogs and then resumed at the previous highest tolerated dose. Results up to the time of dose reduction indicated that CHOP INTEND scores increased for most patients and that the magnitude of the improvement was significantly ($P<0.001$) related to lower patient age at the start of treatment and longer duration of therapy. CHOP INTEND scores declined by 4 points during the dose reduction for 4 patients, improved by 4 points for 3 patients and remained stable for 3 patients. After resumption of the highest tolerated dose (18-27 months of age), 6 patients had a score increase of 7-16 points vs baseline, one patient was stable, and decreased by 4 points. Results to date demonstrate branaplam has good safety and tolerability in SMA type I patients. Continued survival of 62% of treated patients and improvements in CHOP INTEND scores support continued evaluation of branaplam in SMA. Study results also underscore the importance of early intervention and sustained treatment in patients with SMA type I.

http://dx.doi.org/10.1016/j.nmd.2018.06.309

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Phosphorylated neurofilament heavy chain (pNF-H) levels in infants and children with SMA: evaluation of pNF-H as a potential biomarker of SMA disease activity

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Neurofilaments (NF) are structural components of the neuronal cytoskeleton. We examined associations between plasma levels of the phosphorylated heavy isoform of NF (pNF-H) and age, spinal muscular atrophy (SMA) symptomatic status, and survival motor neuron 2 (*SMN2*) gene copy number

in children across the SMA disease spectrum. Blood plasma pNF-H levels were evaluated cross-sectionally in four groups: (1) non-SMA volunteers (age 4-18 years; n=5) (2) infants with presymptomatic SMA (age: 3-42 days; n=25; most likely to develop SMA type I or II), (3) symptomatic infants with infantile-onset SMA (age: 1-9 months; n=121; most likely to develop SMA type I) and (4) symptomatic children with later-onset SMA (age: 2-9 years; n=126; most likely to develop SMA type II or III). Baseline samples from groups 2-4 were obtained before SMA treatment. pNF-H levels were summarized using descriptive statistics. In all non-SMA children, pNF-H levels were <300 pg/mL (range: 12.4-297.5). Among children with SMA, the highest levels were found in Group 2 infants with presymptomatic SMA (median pNF-H levels: 26,300 pg/mL [range: 959-52,900]) followed by symptomatic infants with infantile-onset SMA (median pNF-H level: 15,400 pg/ml [range: 2390-50,100]), then symptomatic children with later-onset SMA (median pNF-H level: 1220 pg/ml [range: 41-6830]). Across the SMA groups, higher pNF-H levels were generally observed among those with 2 *SMN2* copies and declined with advancing age. No clear decline with advancing age was observed among non-SMA children. Overall, mean pNF-H levels in individuals with SMA were higher than those observed in non-SMA children. In individuals with SMA, increasing *SMN2* copy number is generally associated with lower elevations in pNF-H level. pNF-H levels decline with increasing age. These results suggest that pNF-H levels are a biomarker of SMA disease activity.

http://dx.doi.org/10.1016/j.nmd.2018.06.310

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Neurofilament light chain as a potential biomarker in spinal muscular atrophy

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Results from patients with neurodegenerative diseases have shown that neurofilament light chain (NfL) is a sensitive, blood-based marker that can identify patients, aid in prediction of long-term outcomes, and be used to assess effects of treatment. At present, little is known about NfL levels in the blood of patients with spinal muscular atrophy (SMA). Blood samples for assessment of NfL were obtained from 30 healthy adults (24-55 years old), 21 healthy children (1-4 years of age), 18 healthy children (8-10 years old), 18 patients with SMA type III and 2 patients with SMA type II (21-66 years of age), and from 12 patients with SMA type I (2.2-7.6 months of age) who were enrolled in a first-in-human study of branaplam, a small-molecule RNA splicing modulator. Serum NfL levels were measured using the ultrasensitive Simoa HD-I Analyzer. The mean serum level of NfL in healthy adults was 13.4 pg/mL (reference range = 4.6-38.9 pg/mL), 2.5 pg/mL (measured range = 1.7-6.9 pg/mL) for healthy 8-10 year olds, and 4.0 pg/mL (measured range = 1.7-22.9 pg/mL) for healthy 1-4 year olds. NfL levels in adult type II/III patients (7.2 pg/mL, range = 3.9-23.2 pg/mL) were in the lower healthy adult reference range. The mean pre-treatment NfL level in pediatric patients with SMA type I was 443 pg/mL (range = 177-983 pg/mL) and did not overlap with values from healthy pediatric subjects. There was also an inverse correlation between pre-treatment NfL levels and CHOP INTEND scores for the patients with SMA type I. These results suggest that blood NfL levels differentiate patients with SMA type I from healthy children/adults. They may also be correlated with one measure of disease severity. These conclusions are limited by the small number of samples evaluated and the lack of data from healthy pediatric age matched to the patients with SMA Type I. The dynamic course of blood NfL levels in SMA patients requires further study.

http://dx.doi.org/10.1016/j.nmd.2018.06.311

P.264

Circulating microRNAs as biomarkers in Spinraza treated SMA patients

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Spinal muscular atrophy (SMA) is the most common genetic cause of infant mortality, resulting from homozygous deletion in the survival motor euron gene 1 (*SMN1*). MicroRNAs (miRNAs) are a class of small (~22nt) endogenous non-protein-coding RNA molecules that post-transcriptionally regulate gene expression. miRNAs have been shown to play important roles in the regulation of muscle and nervous system development. In a next generation sequencing study, performed in blood samples from patients affected by SMA type II, SMA type III and in healthy controls, we identified 12 miRNAs as significantly dysregulated. With the aim to further analyse if the 12 miRNAs can be used as minimally invasive biomarkers in SMA to monitor disease severity and progression, we carried out real-time PCR analyses of the selected miRNAs in serum from SMA type II (n=7), SMA type III (n=5) and in healthy controls (n=5). Importantly, we also analysed the levels of the selected miRNAs in longitudinal serum/plasma samples of SMA type I patients (n=18) treated with Spinraza, the first FDA and EMA approved antisense oligonucleotide drug for treatment of SMA. A number of the selected miRNAs showed significant differential levels in SMA type I patients in response to Spinraza treatment. Currently, we are correlating the levels of these miRNAs to the clinical outcome of the Spinraza treatment. The results will provide valuable information on the application of the selected circulating miRNAs as biomarkers in SMA and will shed light into the role of these miRNAs in the SMA disease pathogenesis.

http://dx.doi.org/10.1016/j.nmd.2018.06.312

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Patients with spinal muscular atrophy without cardiac disease show elevated cardiac troponin T

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Recent research in adults has shown that skeletal muscles express cardiac isoforms of troponin T (cTnT) in several neuromuscular diseases without cardiomyopathy. We examined whether increased serum cTnT is detectable also in SMA patients and if it correlates with disease severity. The new therapy with Nusinersen has shown to improve motor function. We evaluated whether this treatment has an effect on muscle mass, measured by serum creatinine and whether it changes cTnT. Between 03/2016 and 03/2018 we collected data of 16 patients with SMA (SMA1: 6, SMA 2 or 3: 10). Serum samples were obtained as part of the routine work-up before treatment initiation and prior to each applied dose. The high sensitivity cTnT test (hs cTnT, Roche Cobas) was used. Cardiac disease was excluded clinically, by echocardiography and by measuring cTnI. Serum creatinine (SC) was chosen as surrogate for muscle mass. Disease severity was determined by SMA type and in patients with SMA1 by the need for ventilation within two months after initiating treatment. While all cTnI levels were within the normal range, baseline cTnT in SMA1 patients was 80±39 (range 43-143ng/L) and thus 3 to 10-fold above the upper limit of normal of 14 ng/L. Values of non-ventilated patients were lower than in ventilated patients (p=0,06). SMA2/3 had significantly lower cTnT and cTnT/SC than SMA1 patients (p=0,0002 and p=0,06). After the third application of Nusinersen no significant changes in SC, cTnT, or cTnT/SC could be detected in all SMA groups. As our pilot study shows that cTnT is elevated in all patients with SMA1, it might be useful as a screening tool. As expected, cTnT was correlated with disease severity. We found no support for our hypothesis that Nusinersen improves muscle mass and decreases cTnT. However, small sample size, short follow-up period, and the

lack of a control group make a reliable statement impossible. Further studies with larger patient groups including untreated controls are essential.

http://dx.doi.org/10.1016/j.nmd.2018.06.313

P.266

Neurofilament as a potential biomarker for spinal muscular atrophy: rationale based on animal and human studies

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SMA is an autosomal recessive neuromuscular disorder characterized by degeneration of alpha motor neurons (AHCs) in the spinal cord and brain stem leading to muscular atrophy and weakness. Prognostic and predictive biomarkers are needed to inform SMA treatment. Neurofilaments (NFs) have been proposed as biomarkers in disorders characterized by axonal degeneration, although their clinical utility has not been established. NFs are intermediate filaments uniquely expressed in neuronal cells and are integral components of the cytoskeleton. NFs are differentiated by molecular weight: light (NF-L), medium (NF-M), and heavy (NF-H). About 80% of axonal NFs are highly phosphorylated, conferring resistance to protein degradation. NFs are released into the extracellular fluid during axonal disintegration and are detected in cerebrospinal fluid (CSF) and blood. Advanced detection assays allow robust quantification of NF proteins in the CSF and blood of patients with amyotrophic lateral sclerosis and multiple sclerosis. End stage human SMA pathology is notable for loss of AHCs and ventral root axons, but the timing of degeneration based on disease severity is unknown. Severe SMA mouse models also demonstrate loss of AHCs and denervation of vulnerable muscle groups. In human SMA and mouse models, neuromuscular junctions (NMJs) are structurally immature and contain accumulations of pNFs at the presynaptic terminal, possibly from dysregulation of NF axonal transport with impaired NF degradation. Similar NF accumulations were observed in 70% of diaphragmatic NMJs in SMA Type I infants (age<6 months) versus normal controls. The restoration of NMJ synaptic integrity upon therapeutic restoration of survival motor neuron (SMN) in SMA mice suggests that sufficient SMN expression in the CNS prevents axonal degeneration and NF accumulation in SMA. Assessments of blood and CSF pNF-H levels are promising prognostic and predictive biomarkers for SMA disease activity and/or treatment efficacy.

http://dx.doi.org/10.1016/j.nmd.2018.06.314

METABOLIC MYOPATHIES I

P.267

Local experience of hyperCKaemia in a multidisciplinary neuromuscular clinic

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High creatine kinase (CK) is a major reason to refer for neuromuscular evaluation. It can be a primary or incidental finding, with or without evidence of muscle weakness. CK levels are highly variable between individuals and the upper normal limit is significantly affected by several internal and external factors. HyperCkaemia has a very broad differential including several neuromuscular, metabolic, traumatic, infective and inflammatory. This is a cohort retrospective study of patients referred with or found to have high CK in the neuromuscular clinic at Sydney Children Hospital in the five years 2012 to 2017. We considered the upper limit for CK as 175 IU/L. A systematic search was undertaken of our electronic database system, patient correspondence and referrals. Keywords used for searching were: CK, creatine, kinase, rhabdomyolysis, and dystrophy. Patients who were diagnosed with spinal muscular atrophy, congenital myopathy and myotonic dystrophy were excluded. Data collection included the demographic, clinical, family history and diagnostic work-up. A comparison was undertaken with similar studies in the literature. 750 patients met initial screening criteria. Once all inclusion and exclusion criteria were applied 162 patients were enrolled in our study with 93 having presented after 2012. 33 patients (35%) of those were diagnosed with dystrophinopathies. 33 (35%) had other various diagnoses while 27 (29%) remain undiagnosed. 7 were diagnosed with glycogen storage disease (GSD); 5 Pompe, 2 Mcardle. We further describe the undiagnosed group including extended investigations and molecular genetic tests. The etiologic spectrum of hyperCkaemia in children is rarely found in the literature. In comparison to the few retrospective studies published, our results were overall comparable. Notable was the high incidence of GSD. Using our data we have propose a diagnostic algorithm for hyperCkaemia in children.

http://dx.doi.org/10.1016/j.nmd.2018.06.315

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Reduced skeletal muscle fat oxidation during exercise in an adult with *LPIN1*-deficiency

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LPIN-1 deficiency is an inherited metabolic disease caused by mutations in the gene encoding the enzyme lipin-1 (*LPIN1*). One of its functions is to regulate expression of enzymes in the fatty acid oxidation (FAO). LPIN-1 deficiency is known to cause rhabdomyolysis in early childhood. Very few adults with LPIN-1 deficiency have been described and little is known about the affection in skeletal muscle. We studied a 46-year-old man with LPIN-1 deficiency and 6 healthy controls. He suffered from exercise-induced cramps, pain, fatigue and rhabdomyolysis. All subjects performed a submaximal exercise test at a workload matching 62% of the patient's maximal oxygen uptake. Fat and glucose utilization was assessed by stable isotope technique combined with indirect calorimetry. Another day, he received an infusion of 10% glucose (410 mL x h^-1) and repeated the exercise test. On a third and fourth visit, he was randomized to drink a supplement of glucose (soft drink 2% conc.) or placebo (soft drink: aspartam, acesulfam-K) before and during exercise. The design was double-blinded. We found that total FAO and palmitate rate of oxidation during exercise were lower in the patient than in the controls (431 (SD 79; 303-490) *vs* 1288 (SD 486; 610-2006) μmol x min^-1, and 1.4 (SD 0.3; 1.0-1.9) *vs* 3.1 (SD 0.4; 2.4-3.5) μmol x kg^-1 x min^-1. Carbohydrate oxidation was higher in the patient than in the controls 10.2 (SD 0.6; 9.6-11.0) *vs* 5.3 (SD 3.4; 2.1-10.5) mmol x min^-1. Without glucose, the patient cycled for 36 minutes, but reached 60 minutes with IV-glucose and 46 minutes with oral glucose supplement. His mean self-rated exertion (Borg) during exercise was 15 without glucose, which dropped to 9 with IV- and 11 with oral glucose supplement. Our findings suggest that the patients with LPIN-1 deficiency have reduced FAO during exercise and that glucose ingestion before and during exercise can improve the patients' exercise capacity.

http://dx.doi.org/10.1016/j.nmd.2018.06.316

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Neutral lipid storage disease with myopathy: clinical and genetic spectrum in a large cohort of Chinese patients

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Neutral lipid storage disease with myopathy (NLSDM) are clinically and genetically heterogeneous conditions caused by patatin-like phospholipase domain-containing 2 (*PNPLA2*) gene mutations. We aimed to analyze the clinical and genetic spectrum of NLSDM in Chinese population. The study was conducted by 22 investigators across 6 academic medical centres. We analyzed the clinical course and mutation spectrum in patients with *PNPLA2* mutations. We identified 37 patients with genetically confirmed diagnoses of NLSDM from 33 families. Based on clinical and molecular genetics

findings, we recognized two phenotypes: (1) early onset type started before 10 years old in 3 cases included two patient with hyperCKemia and 1 patient with isolated skeletal myopathy; (2) later onset type started after 10 years old in 34 cases, included 11 cases with skeletal cardiomyopathy, 19 cases with isolated skeletal myopathy and 4 cases with isolated cardiomyopathy. Muscle MRI revealed severe fatty infiltrate in posterior compartment of low extremities. Muscle biopsies showed increase lipid droplet in all cases and rimmed vacuoles in 18 cases, the genetic test of *PNPLA2* identified homozygous mutations in 26 families and compound heterozygous mutations in 7 families. The common mutations of *PNPLA2* gene are splice mutations, point mutations and deletion mutations. The duplication mutation is uncommon. c.757+1G>T, c.245G>A and c.187+1G>A are frequently observed. Five novel mutations were detected. The mutations distributed diffusely along the whole gene of *PNPLA2* without phenotype clustering phenomena or genotype-phenotype association. We verified clinical heterogeneity of NLSDM, which define two clinical types. HyperCKemia often appeared in early-onset type while cardiomyopathy are common in the late-onset type. Genotype-phenotype association were not identified.

http://dx.doi.org/10.1016/j.nmd.2018.06.317

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Lipid storage disorder - Proteomic analysis of skeletal muscle mitochondria

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Defects in fatty acid metabolism leads to a heterogenous group of inherited metabolic disorders due to impairment of mitochondrial beta oxidation pathway resulting in accumulation of lipid droplets within the muscle fibers. The molecular events underlying impaired lipid storage and mitochondrial changes have not been completely understood. Hence, biochemical analysis of mitochondrial function on skeletal muscle biopsies of five patients diagnosed based on morphological findings as lipid storage disorder (LSD) was carried out. Protein profiling of the muscle mitochondria using high throughput mass spectrometry revealed impaired metabolic processes contributing to mitochondrial dysfunction. Among the 266 mitochondrial proteins identified, 98 proteins were differentially expressed, with 38 up-regulated (≤1.5-fold) and 60 down-regulated (≤0.7-fold) proteins in all cases compared to control. 68 % of over-expressed proteins were linked with the metabolic pathways including oxidative phosphorylation and fatty acid (FA) metabolism. Similarly, 63 % of the proteins down-regulated were linked with metabolic pathways including amino acid metabolism. Analysis of the proteomic data for clustering of related genes in specific pathways showed that the differentially regulated proteins were predominantly part of FA metabolism (n=16), respiratory complexes (RC) and their assembly (n=17) and TCA cycle (n=16). While, a few proteins linked with antioxidant function (n=6) and mitochondrial permeability transition pore (n=3) were differentially expressed. Most of the proteins involved in FA metabolism (14 out of 16) and TCA cycle (15 out of 16) proteins were down regulated compared to control. In addition, other proteins (n=40) with physiologically relevant mitochondrial functions including mitochondrial architecture and metabolism showed differential regulation. We conclude that impaired fatty acid metabolism, Krebs cycle, oxidative phosphorylation and redox leads to mitochondrial dysfunction in LSDs.

http://dx.doi.org/10.1016/j.nmd.2018.06.318

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MicroRNA dysregulation and signalling in lipid storage myopathies

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The main causes of excessive accumulation of triglycerides in skeletal muscle are carnitine deficiency, ETF-dehydrogenase deficiency or riboflavin responsive multiple acyl-CoA dehydrogenase deficiency and neutral lipid storage myopathy (NLSDM) due to mutation of *PNPLA2* gene, encoding for adipose trygliceride lipase. MicroRNAs are small non-coding RNA and they are negative regulators of gene expression. We investigated their role in various types of LSM. We observed three LSM patients caracterized by heterozygous mutation in ETF- dehydrogenase associated to muscle carnitine deficiency, three patients pertaining to a NLSDM family. We measured myo-microRNAs in serum (miR-1, miR-206, miR-133a, miR-133b). We obtained muscle MRI/CT scans in these patients and compared muscle imaging with elevation of myomiRNAs respect to controls. In patients we found the elevation of myo-miRNAs and we investigated the correlation of muscle mass found by imaging. Alterations are particularly evident in posterior thigh muscle of all patients with ETF-deydrogenase mutation. While some conditions were under treatment, NLSDM cases were without a specific treatment.In muscle biopsies we observed lipid storage in muscle. Jordan's anomaly (i.e. lipid droplets in leukocytes) was observed in three patients of NLSDM family, they also exhibited a marked elevation of myo-microRNAs in serum in the range of 10-20 fold that correlated in two male brothers with distal muscle atrophy and in the sister with hepatosteatosis, two of them had an asymmetric upper or lower muscle distal atrophy. In ETF-dehydrogenase deficiency myo-microRNA profile was less upregulated but still inversely correlated to muscle mass found in imaging studies. The myoRNAs represent in NLSDM and other LSM an useful indicator of muscle atrophy. In these metabolic myopathies it is possible to monitor their evolution during natural history, physical treatment, drug or nutritional trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.319

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No effect of triheptanoin on exercise performance in patients with McArdle disease - a double blind placebo-controlled crossover study

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Patients with McArdle disease have blocked muscle glycogen breakdown due to an inherited defect myophosphorylase. This causes exercise intolerance with muscle pain, contractures and rhabdomyolysis. McArdle patients cannot increase fat oxidation to fully compensate for the energy deficiency due to a slow turnover in the tricarboxylic acid cycle (TCA). Metabolism of the 7-carbon fatty acid, triheptanoin, generates acetyl-CoA and propionyl-CoA, which enter the TCA and can therefore potentially boost fat oxidation in McArdle patients. In this double blind, placebo-controlled, crossover study we included 22 patients. Participants completed two 2-week treatment periods with a diet on triheptanoin or placebo oil (1g × kg-1 × day-1) separated by 1-2 weeks of washout. At baseline and at the end of the treatment periods, patients performed 20 minutes of submaximal exercise on a cycle ergometer followed by increments until exhaustion. Blood metabolites were measured every 10 minutes and exchange of O2. and CO2 was measured breath-by-breath. Nineteen patients completed the trial and qualified for data analysis. The patients had similar mean heart rates during submaximal exercise with triheptanoin (120±SD16 bpm) and with placebo treatment (121±SD16 bpm). Submaximal respiratory quotients were the same with triheptanoin (0.82±SD0.05) and placebo (0.84±SD0.03). They reached the same maximal workloads with treatment vs. placebo (105±SD38 vs. 102±SD31 Watts) and maximal oxygen uptake (1938±SD499 *vs.* 1977±SD380 mL × kg-1 × day-1). Blood glucose dropped with exercise to 4.6±SD0.8 *vs.* 4.4±SD1.0 mM and there was no difference in the production of ammonia with exercise (167±SD88 *vs.* 202±SD111 μM). Biochemical analyses of plasma TCA intermediates and fatty acids are ongoing. These preliminary data show no

effect of triheptanoin treatment on exercise capacity and tolerance or muscle energy metabolism in McArdle patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.320

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Delineating the phenotypic spectrum of *PGK1*-associated phosphoglycerate kinase deficiency: the French experience

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Phosphoglycerate kinase (PGK) deficiency is a rare X-linked metabolic disorder caused by mutations in the *PGK1* gene. Patients usually develop various combinations of non-spherocytic hemolytic anemia (NSHA), myopathy, and neurological disorders. In this study, we analyzed the phenotypic features of 3 French unrelated patients with PGK deficiency. The first case was a 32-year-old patient who presented with mental retardation, microcephaly, bilateral ophtalmoplegia, pes cavus, and severe chronic axonal sensorimotor polyneuropathy since childhood. Myopathy, exercise intolerance, rhabdomyolysis and NSHA were not observed. CK levels were normal, and muscle biopsy found neurogenic abnormalities. Muscle PGK1 enzymatic activity was decreased, and the never-described hemizygous c.323G>A *PGK1* variation was found. The second case was a 71-year-old patient who presented with recurrent exertional rhabdomyolysis since childhood. He had chronic hyperCK-emia and post-exercise hyperammonemia. He had neither mental retardation, nor NSHA. Erythrocyte PGK1 enzymatic activity was decreased, and the previously reported hemizygous c.943G>A *PGK1* variation was found. The third case was a 48-year-old patient with NSHA, retinitis pigmentosa and mental retardation since childhood. He developed seizures at age 5 years, Parkinsonism at age 37 years, and he had no myopathy. Muscle biopsy was normal, and brain MRI showed cerebral ischemic sequelae. Erythrocyte PGK1 enzymatic activity was decreased, and the previously reported hemizygous c.491A>T *PGK1* variation was found. This study demonstrates the wide phenotypic spectrum of PGK deficiency. In our series, one patient presented with a "pure" neurological disease, one patient presented with a "pure" myopathy and one presented with neurological disease plus hemolytic anemia. Clinical variability in PGK deficiency is unexplained, and environmental, metabolic, genetic and/or epigenetic factors probably contribute to the phenotype.

http://dx.doi.org/10.1016/j.nmd.2018.06.321

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Heterozygous mutation in *ISCU* associated with recurrent rhabdomyolysis

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Hereditary myopathy with lactic acidosis and myopathy with deficiency of succinate dehydrogenase and aconitase are variants of a recessive disorder characterised by childhood-onset early fatigue, dyspnoea and palpitations on trivial exercise. The disease is non-progressive, but life-threatening episodes of widespread weakness, metabolic acidosis and rhabdomyolysis may occur. So far, this disease has been molecularly defined only in Swedish patients, all homozygous for a deep intronic splicing affecting mutation in *ISCU* encoding a scaffold protein for the assembly of iron-sulfur (Fe-S) clusters. We report here the case of 17 years-old girl native from French Caribbean Islands who presented with acute diffuse muscle pain, facial edema, and mild proximal muscle weakness (3/5). Medical history revealed exercise intolerance and three episods of rhabdomyolysis (maximum CK levels at 74,000; 20,000 and 3,000 UI/L) without renal failure during the last two years. Blood testing showed markedly increased CK levels (195,560 UI/L, normal<200) and lactic acidosis. Muscle biopsy showed myofiber anisodiametry, and scaterred basophilic fibers. Immunohistochemical study showed numerous NCAM-positive regenerating fibers, most often grouped in areas. MHC-1 immunostaining disclosed a few randomly distributed positive fibers. C5b-9 immunostaining showed 'rabbit poop' sarcolemmal complément deposits. Perls (prussian blue) stain showed some fibers with mild punctuate accumulation of iron (Fe3+). Genetic analysis (NGS) disclosed compound heterozygous mutation c418+382G>C in *ISCU*. Present case indicates that *ISCU* mutations can be considered as a possible cause of recurrent rhabdomyolysis. In the context of rhabdomyolysis, histopathological techniques should include Perls stain to detect suggestive myofiber iron accumulations.

http://dx.doi.org/10.1016/j.nmd.2018.06.322

P.275

A case of late-onset multiple acyl-coenzyme: a dehydrogenase deficiency in a young female of Turkish descent

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We describe an unusual case of late-onset multiple acyl-coenzyme A dehydrogenase deficiency (MADD), a rare autosomal recessive metabolic disorder caused by mutations in either electron-transfer-flavoprotein alpha or beta polypeptide or electron-transfer flavoprotein dehydrogenase (*ETFDH*) that effects mitochondrial electron transfer and metabolism of fatty acids, amino acids, and choline, as well as the development of clinical symptoms and morphological findings over a period of 2 years. In the late-onset form in adolescents and adults, muscular or cardiac symptoms or episodic vomiting are usually first symptoms suggesting MADD. For 3 months a 27-years old female of Turkish descent recognised muscle pain and weakness, at admission she had difficulty lifting her arms, raising her head and walking long distances. She had lost 8 kg of weight, but vomiting was denied. Serum CK was elevated to 1100 U/L. A 1st muscle biopsy showed only mild vacoular myopathy with signs of lipid accumulation between muscle fibres but no mitochondrial damage in EM. About one month later she was unable to stand or walk (MMT score 2/5 in legs, 2-3/5 in arms), had lost further weight, and serum CK levels had increased to 1800 U/L. A 2nd biopsy showed numerous necrotic fibres, all in the same stage of degradation, suggesting toxic myopathy, and type I fibres with large cytoplasmic vacuoles containing lipids. EM revealed mitochondria with paracristalline inclusions. No noxious agent could be identified. Respiratory chain enzyme analysis showed reduced activity of complexes I-IV, but mitochondrial DNA analysis was unremarkable. Yet, treatment with coenzyme Q10 was started with only slight clinical improvement. In a 3rd biopsy taken about 5 months later no signs of lipid storage myopathy were evident histologically, but EM persistently showed lipid accumulation and pathologic mitochondria. About 2 years after onset of the illness, genetic analysis identified a compound homozygous missense *ETFDH* gene mutation: p.L377P (c.1130T>C). This variant has so far only been described in a Turkish infant diagnosed with MADD at the age of 7 months. Riboflavin and L-carnitin led to significant clinical improvement and decrease of serum CK levels in our patient. The diagnosis of MADD is often difficult when symptoms are nonspecific and it could commonly be misdiagnosed, so genetic test may be essential.

http://dx.doi.org/10.1016/j.nmd.2018.06.323

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Electron transfer flavoprotein-ubiquinone oxidoreductase defect and FAD homeostasis in riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency

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Riboflavin-responsive multiple acyl-CoA dehydrogenation deficiency (RR-MADD) is an inherited fatty acid metabolism disorder mainly caused by genetic defects in electron transfer flavoprotein-ubiquinone oxidoreductase (ETF-QO). This disease was reported to be more common in Chinese population accounting for 3-5% of muscle biopsies from several neuromuscular centers in China. The variant ETF-QO protein folding deficiency, which can be corrected by therapeutic dosage riboflavin supplement, has been identified in HEK-293 cells and is believed to be the molecular mechanism of this disease. To verify this hypothesis *in vivo*, we generated *Etfdh*(h)A84T knock-in mice. Tissues from these mice as well as muscle biopsies and fibroblasts from 7 RR-MADD patients were used to examine the FAD concentration and ETF-QO protein amount. All of the homozygote knock-in mice (*Etfdh*(h)A84T/(h)A84T, KI/KI) were initially normal. After fed by a high fat and vitamin B2 deficiency (HF-B2D) diet for 5 weeks, they developed weight loss, movement ability defects, muscle and liver lipid storage and elevated serum acyl-carnitine levels, which is clinically and biochemically similar to RR-MADD patients. Both ETF-QO protein and FAD concentration significantly decreased in the tissue of HF-B2D-KI/KI mice and in cultured fibroblasts from RR-MADD patients with low dose riboflavin supplement. After riboflavin treatment, ETF-QO protein increased in parallel with elevated FAD concentrations, but not related to mRNA levels. For the first time, we successfully developed an RR-MADD mice model, making possible research into the pathomechanism of this disease. Moreover, we confirmed that both *ETFDH* mutations and FAD homeostasis disturbances exist in RR-MADD *in vivo*. Supplementation of riboflavin may stabilize variant ETF-QO protein by rebuilding FAD homeostasis.

http://dx.doi.org/10.1016/j.nmd.2018.06.324

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A curable myopathy manifesting as exercise intolerance and respiratory failure

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Few forms of severe genetic myopathy can successfully be treated, but the diagnosis may be challenging. Here, we present a patient with exercise intolerance and normal noninvasive exams that had a reversible metabolic myopathy. Case report. A 32-year-old white female presented with a 2-year history of progressive exercise intolerance and lower-limb myalgia. No relevant familial history was reported and the patient's motor development was unremarkable. A mild weakness limited by pain was noted in the upper and lower limbs, as well in the axial muscles. Several serum CK measures, echocardiography, thorax computed tomography, abdominal ultrasound and electromyography/nerve conduction study (EMG/NCS) were normal. Serum acylcarnitine profile was unremarkable and screening for Pompe's disease was negative. As the patient remained with fatigue and myalgia, a muscle biopsy was done, and it revealed a vacuolar myopathy with massive lipid droplets, predominantly in type 1 fibers. During the investigation, the patient presented rapid deterioration of respiratory insufficiency requiring noninvasive mechanical ventilation, dysphagia and a marked weakness with dropped head. She received empirically riboflavin, coenzyme-Q10, and L-carnitine in high doses. After 3 weeks, she presented a dramatic recovery with normalization of the motor exam. The molecular study identified compound heterozygous pathogenic mutations in the electron transfer flavoprotein dehydrogenase (*ETFDH*) gene, and the diagnosis of multiple acyl-CoA dehydrogenase deficiency (MADD) was made. Discussion. MADD is an autosomal recessive inherited disorder of fatty and organic acid metabolism caused by mutations in genes involved in electron transfer to the respiratory chain by flavoproteins. MADD must be considered in patients with progressive dyspnea with exercise intolerance, even if CK, acylcarnitine profile and EMG are normal, as this condition is highly responsive to riboflavin supplementation.

http://dx.doi.org/10.1016/j.nmd.2018.06.325

REGISTRIES AND CARE OF NEUROMUSCULAR DISORDERS

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How can we ensure children with neuromuscular conditions achieve personally meaningful futures?

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Given advances in medical care, it is critical that children with neuromuscular (NM) conditions develop self-determination (SD) so that they can make choices that ensure a meaningful, healthy and productive future. Children with disabilities often have fewer opportunities to develop SD i.e. using knowledge and beliefs to engage in goal-directed, self-regulated and autonomous behavior. Underpinned by SD theory, solution focused coaching-pediatric rehabilitation (SFC-Peds) is a strengths-based, person-centered intervention that builds on the child's capacities and enables them to identify personally meaningful goals, generate attainment strategies and achieve their 'preferred future'. However, we do not know what 'dose' is appropriate. Eleven children (9 M, 2 F; range 12-17 yrs) with NM conditions participated in SFC-Peds sessions delivered via videoconferencing. Participants were randomized to receive either 1 SFC-Peds session (n=5) or 5 sessions (n=6). The Canadian occupational performance measure (COPM) was used to identify occupational performance issues and measure changes in performance and satisfaction. Goal attainment scaling (GAS) was used to develop personally meaningful goals and assess goal attainment. Interim analysis shows overall clinically significant changes (i.e. >2 points) in performance and satisfaction for 8 participants (mean change 3.5, SD 2.2 and mean change 3.1, SD 2.8 respectively) on the COPM. Eight of 14 GAS goals were attained. There were no differences between the two groups; however, numbers are small. The majority of goals focused on psychosocial health, including coping with academic pressures, feeling comfortable using a wheelchair, joining a group at school, communicating with peers, learning how to make friends and participating in recreation activities. Results suggest that SFC-Peds can help children with NM conditions identify and achieve personally meaningful goals, and therefore may potentially build SD.

http://dx.doi.org/10.1016/j.nmd.2018.06.326

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A four year review of a Canadian pediatric neuromuscular clinic

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A variety of patients are evaluated in neuromuscular clinics worldwide. With evolving technologies, genetic confirmation of neuromuscular cases is improving. In an effort, to evaluate the diagnostic efficacy of the pediatric neuromuscular clinic at the Hospital for sick children in Toronto, Canada, a review of the clinical database over an approximately four year period was undertaken. The clinical database was reviewed for patient numbers, diagnostic testing results and confirmed diagnoses. Interesting cases will also be highlighted. 75 patients were evaluated during this time period, mostly through the outpatient clinic. Of these patients, approximately 50% have genetic confirmation. The breakdown of confirmed diagnoses is as follows: muscular dystrophy 20%, congenital muscle disease 20%, rhabdomyolysis/metabolic conditions 15%, spinal muscular atrophy 12%, Charcot-Marie-Tooth disease 12%, acquired/autoimmune 5%, arthrogryposis 5%, myotonic dystrophy 4%, congenital myasthenic syndrome 4%, channelopathy 4% and movement disorders 2%. For diagnostic testing, muscle biopsy is still used as a first line diagnostic tool in the majority of congenital muscle disease cases, while it is rarely used in the muscular dystrophies, particularly the dystrophinopathies. Genetic confirmation was obtained through panel or targeted testing for the majority of patients; whole exome sequencing was only used to confirm the diagnosis in 3 cases. The diagnostic yield in our clinic is relatively high. Panel and targeted testing is still the best test for genetic

confirmation. Further analysis of the undiagnosed cases is needed to identify the gaps in diagnostic confirmation. There is a sample bias as there are other neuromuscular clinics in our hospital that are not captured by this analysis.

http://dx.doi.org/10.1016/j.nmd.2018.06.327

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Registry of neuromuscular genetic disorders in Russia

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Neuromuscular disorders are widespread all over the globe. Creation of registers for patients with specific diseases unites patients into unique groups. This allows scientists to determine the incidence and prevalence of diseases in specific populations and regions. Registries help to identify individual needs of patients and improve the quality of life, stimulate the development of basic science and molecular genetic technologies, which in the near future will be able to cure patients with neuromuscular disorders. About 4 years ago we started to collect blood and data of the DMD and SMA patients in Russia and gather them in 2 disease specific Genetic Registers. To the date we collected more than 550 patients with DMD and BMD; more than 550 patients with different types of SMA. Since the 2018 we started the new project of Neuromuscular Genetic Registry in Russia. The aim is to collect different data of patients (clinical, genetics, muscle biopsy, MRI, etc.) also with collecting patient's blood. We have concentrated on several diseases that are most common in Russia: congenital muscular dystrophy type 1A (*LAMA2* gene), collagen VI disorders (Bethlem and Ullrich CMD), patients with LGMD2I (*FKRP* gene), patients with LGMD2A (*CAPN3* gene), patients with LGMD2B and Myoshi dysferlinopathies, patients with Facioscupulohumeral muscular dystrophy, patients with *RYR1* mutations and other rare diseases. In Russia there are hundreds of patients that still have no genetics and proved diagnosis. This is making them very far from the future treatment. We include all neuromuscular patients in our Neuromuscular Genetic Registry. Collecting blood and information will provide additional information about the natural history of the disorders that possibly in future will help scientists to understand better pathogenesis and other factors that could influence on the course of the disease. Also clinical trials will provide to our patients advanced treatment.

http://dx.doi.org/10.1016/j.nmd.2018.06.328

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Participation and its determinants in children with neuromuscular disease

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Improving participation is one of the most important goals of any intervention in care of children with neuromuscular disease. The child and adolescent scale of participation is one of the few tools available to evaluate participation in childhood. The aim of this study was to evaluate participation and its determinants in a sample of children with neuromuscular diseases. The CASP was filled by parents during a regular follow-up visit of their child (3 to 18 y) in two French reference centers for rehabilitation of neuromuscular disease. The CASP measures the extent to which children participate in home, school, community, and in community living activities as reported by family caregivers from 20 items using a four-point Likert scale (from 4: aged expected; to1: unable), or 'not applicable'. Correlations were analyzed between participation and demographic and clinical factors (motor ability as assessed by the motor function measure (MFM), age). Inclusions are still ongoing. At 4 April 2018, 58 parents filled the CASP, mean age at assessment: 11 y (SD: 3.6), 40 boys, 20 DMD, 7 SMA, 21 others. Mean total CASP score was 85.1% (SD: 12.4). The better subscore was subscore "School" 89.2% (SD: 10.9) and the worst was subscore "Activity" 78.8% (SD: 20.1). Total CASP scores tend to be correlated with MFM (r=0.45) but not with age (r=0.07). Concerning CASP subscores, the higher correlation with MFM was observed for subscore "Home" (r=0.59), and the worst correlation was found for subscore "School" (r=0.13). Participation is reduced in children with neuromuscular disease. The CASP seems to be able to evaluate participation in this population and should help to improve rehabilitation care of these children. The inclusion of a greater population will allow us to evaluate the internal consistency of the CASP and to perform an exploratory factor analysis to validate the French version of the CASP in this population.

http://dx.doi.org/10.1016/j.nmd.2018.06.329

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Drop-out in longitudinal natural history studies in neuromuscular diseases: rates and main rationale

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Prospective studies with standardized evaluations provide one of the strongest methodologies for studying the progression of neuromuscular diseases and constructing clinical development plan to evaluate new therapies. Drop-out is a major methodological problem of longitudinal studies. It may represent an attrition bias and lead to erroneous conclusions if participants who stay in a study differ from those who dropped out. Here, we present drop-out rate and reasons for dropping-out in prospective studies in neuromuscular diseases and we study predictive factors. We focused on 4 prospective and longitudinal natural history studies conducted or coordinated in our center in three neuromuscular diseases: Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA) and myotubular myopathy (MTM). We studied factors previously shown as predictors of attrition such as sociodemographic variables including age at enrollment, gender, patient's native language as compared to center's one, in- or outpatient. We also studied factors such as the clinical status of the patient (ambulatory, respiratory and feeding status), the study design (duration of the study, visit frequency, number of assessment) and the existence of concomitant therapeutic clinical trials or market approved treatments. On 31st December 2017, the median duration of the studies were 4.0 years [2.6 - 6.2]. The probability of drop-out occurrence during the first year was 11.3% (12.3%, 10.8% and 9.9 % in SMA, DMD and MTM patients respectively). Among the eighty-two patients who dropped out over 188 enrolled, 54% withdrew to be enrolled in a therapeutic study, 7% because of death and 24% withdrew for different reasons (i.e. lack of motivation, distance from the center or fatigue). The understanding of dropping out and precise estimation of its rates allows better sample size estimation of natural history studies and may help identifying patients at risk of dropping out at early stage of the study.

http://dx.doi.org/10.1016/j.nmd.2018.06.330

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The development of a Brazilian Portuguese version of the activity limitations scale (ACTIVLIM)

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Daily activity limitations of patients with neuromuscular disorders are measured by ACTIVLIM. The scale measures the ability to perform the daily activities, whatever the strategies involved to compensate for the upper and/or lower limbs impairments. ACTIVLIM has been validated for the assessment of adults between 16 and 80 years of age. The scale is available in French, Dutch and English and evaluates the functional independence of patients by their self-report (easy, difficult or impossible to perform each activity). The translation was authorized by one of the authors of the original scale. ACTIVLIM was translated and adapted to Brazilian Portuguese. Two proficient translators developed ACTIVLIM Brazilian Portuguese ver-

sions independently (translation 1 and translation 2). Then, a consensus was generated by both translators (translation consensus). After that, based on the translation consensus, two other translators developed two versions in English (back translation 1 and back translation 2). Another meeting established the consensual version of back translations in English (back translation consensus). This final version was compared with the original English version, to detect possible semantic differences. The final version was also revised by three physical therapists with experience in neuromuscular disorders. As suggested by one of the authors of the original scale, cultural adaptations were proposed by the Brazilian physical therapists. The items about the difficulty in "taking a bath" and "stepping out of a bath tube" were considered unsuitable, because Brazilians usually take a shower, instead of a bath (in a bath tub). These items were adapted to "getting in a swimming pool" and "getting in the shower stall". The final Brazilian Portuguese version of ACTIVLIM was considered feasible and will be tested with patients with neuromuscular diseases.

http://dx.doi.org/10.1016/j.nmd.2018.06.331

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Quantifying activity changes of neuromuscular patients using the ACTIVLIM questionnaire: a 5-years longitudinal study

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The ACTIVLIM questionnaire was developed to measure global activity performance of neuromuscular patients (NMPs). It also has the potential to assess real life improvement resulting from new coming therapies. For this purpose, long term follow-up data are mandatory. Such data are currently absent from the literature. The aim of the present study is to compare ACTIVLIM measures of NMPs from the Belgian neuromuscular disease registry (BNMDR) between years 2011 and 2015. Data from 1064 NMPs who completed the ACTIVLIM questionnaire in 2011 and 2015 were extracted from the BNMDR. RUMM 2030TM was used to obtain their global activity performance level. The Wilcoxon signed rank tests and paired t-tests were used to compare ACTIVLIM measures obtained in 2011 and 2015 for the whole sample and for the 9 most prevalent diseases in BNMDR. In the whole sample, 64% of NMPs showed a deterioration of their activity ($p \leq 0.012$; effect size (ES) =-0.32). The magnitude of deterioration was the most important for Duchenne muscular dystrophy (74% of them deteriorated; $p<0.001$; ES=-0.46), limb-girdle muscular dystrophy (74% deteriorated; $p<0.001$; ES=-0.44), hereditary spastic paraplegia (66% deteriorated; $p<0.001$, ES=-0.41), and amyotrophic lateral sclerosis (69% deteriorated; $p<0.001$; ES=-0.40). Deterioration was significant but less important for myotonic dystrophy type 1 (63% deteriorated; $p<0.001$; ES=-0.32), spinocerebellar ataxias (67% deteriorated; $p<0.001$; ES=-0.31), facioscapulohumeral dystrophy (59% deteriorated; $p=0.016$; ES=-0.23), and hereditary motor and sensory neuropathy (60% deteriorated; $p<0.001$; ES=-0.22). For patients with chronic inflammatory demyelinating polyneuropathy (CIDP), no deterioration was observed ($p=0.939$; ES=-0.01). This is the first study focusing on activity level of NMPs using ACTIVLIM across a 5-year period. As expected, most patients showed deterioration in their activity. CIDP patients showed a different evolution of their global activity performance.

http://dx.doi.org/10.1016/j.nmd.2018.06.332

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Validation of the Brazilian Portuguese version of the motor function measure - short form (MFM-20) for neuromuscular diseases in children from two to seven years old

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Neuromuscular disorders (NMD) include a large number of conditions involving muscle weakness. There is a lack of tools to assess motor function in young children with NMD. The Motor Function Measure (MFM-32), validated in Brazil as MFM-P, monitors the severity and progression of motor function in patients with NMD, from six to sixty years old. As this version was not validated in children under six years of age, the authors of the original version, from Pediatric Reeducation Service L'Escale (France), developed the Motor Function Measure - Short Form (MFM-20), designed for children from two to seven years old. The aim of this study was to test the reliability and validity of MFM-20 in Brazilian Portuguese. The translation of MFM-20 was performed by the same researchers that translated MFM-32 in Brazil. After a pretest in a sample of five subjects, the translated version was applied with twenty-six children with NMD. To verify the inter-rater reliability, the Wilcoxon Test compared the scores given within one-week interval and the Student's Test compared the scores given by two physical therapists at the first day. To verify the converging construct validity between MFM-20 and Hammersmith Motor Functional Scale (HMFH), Barthel's Index (BI) and Vignos and Brooke Scale (VBS), as well as the discriminating construct validity between MFM-20 and the Medical Research Council Scale (muscular strength), Pearson correlation tests were applied. Twenty six patients with mean age 4.6 ± 1.5 years old were included in this study, with the following clinical diagnosis: Duchenne muscular dystrophy (n=9), congenital muscular dystrophy (n=5), congenital myopathy (n=6) and type 2 spinal muscular atrophy (n= 6). The reliability analysis demonstrated good reproducibility for intra-rater on the first day (35.8±8.8) and after one week (37.0±9.0); p= 0,050, and good inter-rater reproducibility (examiner 1: 35.8±8.8 and examiner 2: 35.1±9.2). The converging validity analysis demonstrated good correlation between MFM-20 and HMFS, VBS and BI, with correlation coefficients: 0.907, -0.918 and 0.797, respectively. The discriminating validity analysis demostrated positive correlation between MFM-20 and Medical Research Council, with a correlation coefficient 0.873. The Brazilian Portuguese version of MFM-20 showed validity, representing advances for patients in Brazilian's centers.

http://dx.doi.org/10.1016/j.nmd.2018.06.333

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A new minimally invasive fusionless technique that avoid vertebral arthrodesis for neuromuscular scoliosis

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Spinal deformities are common in NM diseases. Conventional treatment involves bracing, followed by spinal instrumented fusion. Growing rod techniques are increasingly advocated but fusion is usually required at the end of the growth period. To report the results of an alternative technique using a minimally invasive fusionless surgery. It is based on the progressive correction of the deformities with proximal and distal fixation and on the reliability of the pelvic fixation using ilio-sacral screws on osteoporotic bones. A retrospective study was performed in the first 34 children with neuromuscular disorders who underwent surgical correction of scoliosis using this new fusion-less technique, from 2011 to 2015. The series included children affected with neuromuscular disorders, including 24 SMA, 7 CMD (3 Ullrich, 2 alpha-DG, 1 *LAMA2*, 1 *LMNA*), 2 Duchenne and 1 SG. Cobb angle and

pelvic obliquity were measured before and after initial surgery, and at final follow-up. Complications were reviewed. All patients had a follow-up over 2 years from initial surgery, more than 6 years for the oldest. Mean age of first surgery was earlier in SMA than myopathy (10 vs 13y). Ten patients (5 SMA and 5 myopathy) were already at a trunk mature skeletal stage at their first operation (11- 14y). No definitive spinal fusion has been planned until now in any patient. Radiological follow-up showed signs of a progressive spontaneous consolidation of the vertebral bodies, with visible degeneration of disc spaces and articular processes in parallel with a continuation of vertebral growth in the oldests patients. Bipolar distraction produced by the instrumentation seemed also to enhance the growth of the spine in length and width. Concerning scoliosis correction, Cobb angle was significantly improved from av 88° ±24 before surgery to av 34 ±15 at latest follow-up. Pelvic obliquity improved from av 26° ± 18 before surgery to av 6°± 5 at latest follow-up. Global complication rate was significantly decreased compared to other fusionless techniques (9%mechanical, 15% infectious). This new fusionless technique offers important advantages for patients affected of NM scoliosis, in particular the absence of need of final arthrodesis. Its use is not only opened to young children but may replace invasive definitive fusion even in mature skeletal stages.

http://dx.doi.org/10.1016/j.nmd.2018.06.334

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Mechanically assisted cough: how to keep it simple

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Mechanical insufflation - exsufflation (MI:E) is a life extending method in neuromuscular patients with cough insufficiency. It supports airway clearance to prevent mucous retention, atelectasis and pneumonia. Some neuromuscular centers (NMC) are still unexperienced and hesitant in its use. In our pediatric NMC we have thus developed a standardized approach to facilitate practical use. Initial routine was based on literature and experience of two large centers. We use only one type of device. MI:E is introduced when cough peak flow is <50% of age-related reference, in ventilated patients and in case of clinical obvious cough insufficiency. We preset 3 different modes for home use. Mode 1 provides only insufflation for daily lung volume recruitment in health. In mode 2 in- and exsufflation are preset for airway secretions or SpO2<95%. In mode 3 expiratory oscillation during exsufflation is added for sticky secretions. Durations of in- and exsufflation are increased with age while pressures for in- and exsufflation are fixed at 30-35 cmH_2O and -40 cmH_2O. Staff, patients and caregivers are trained in MI:E to use modes depending on health condition of the patient and for emergencies. Retraining is performed regularly. This standardization facilitated teaching of staff, patients and caregivers in MI:E in our and other Austrian NMCs. Acceptance was rapid. Only 10% required adaptations to optimize efficacy. Proactive initiation and empowerment of patients and caregivers through training in applying those 3 different modes prevent emergencies. In 60 patients initiated using MI:E during 4 years no pneumothorax occurred. Only 2 SMA 1 patients died due to severe course of disease. This model could be used as a guide for NMCs with limited specialized staff for and expertise in respiratory management. Further investigations regarding the effects on clinical end points like hospitalisation rate and survival are needed.

http://dx.doi.org/10.1016/j.nmd.2018.06.335

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Diagnosis, management and outcome of severe congenital onset neuromuscular disorders in a series of 50 infants

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Congenital onset neuromuscular disorders (NMD) are a heterogeneous group of diseases including congenital muscular dystrophies (CMD), congenital myopathies (CM), congenital myotonic dystrophy, congenital myasthenic syndromes (CMS) and metabolic myopathies. These are characterised by onset before or at birth. Final molecular diagnosis is often delayed causing a direct impact on outcome of these children. We aimed to clinically characterise a series of infants less than three months old referred to the neuromuscular service from 2010 to 2017 and study their outcomes to develop standards of care for this group. Only those with severe symptoms were included. 50 infants less than three months-old were seen. Majority were male (68%). Antenatal problems were noted in 38 (76%). 29 (58%) had hypotonia, 28 (56%) weakness and 32 (64%) had contractures. Feeding difficulties were noted in 37 (74%) and respiratory insufficiency in 39 (78%). Contractures and weakness were more prevalent among those with a final NMD diagnosis (contractures: 72% *vs* 56%; weakness: 72% *vs* 40%). None with a final non-NMD diagnosis had contractures. CK was abnormal in 3 (6%), Neurophysiology was abnormal in 39 (93%).Muscle biopsy was the single most helpful investigation. This was abnormal in 29 and diagnostic in 13 (39%). Final molecular diagnosis was achieved in 27(54%) at a mean age of 5.5 months, confirming a NMD in 25 (50%; CM: 14 (28%); CMD: 7 (14%); SMA: 2 (4%); CMS: 2 (4%)). 21 (41%) remain undiagnosed despite extensive testing. 22 (44%) died with 12 unexpected deaths. 20 (68%) required NG feeding/gastrostomy and 14 (48%) are on respiratory support. At last follow-up only 5 had achieved independent ambulation. Our data highlights weakness and contractures as the key features of congenital NMD. Muscle biopsy is recommended early to minimise delays in diagnosis. This group of disorders is associated with high morbidity and mortality and early introduction of respiratory surveillance is recommended.

http://dx.doi.org/10.1016/j.nmd.2018.06.336

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Patients experience of diagnosis of a genetic muscle disorder

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Little is known about what patients experience when being diagnosed with a genetic disorder and which factors may influence their experience. In order to inform policy on the delivery of genetic diagnoses and improve the experience for patients with rare genetic disorders patients with genetic muscle disorders including; muscular dystrophies, myotonic dystrophy, Pompe disease, ion channel muscle disorders and other myopathies, were asked to describe their experience. A questionnaire designed to elucidate the patients' experience of receiving their diagnosis was included as part of the assessment of impact of a large nationwide population-based study of the prevalence and impact of genetic muscle disorders, MD Prev. The questionnaire asked firstly whether the patient had a genetic diagnosis, what their experience was in relation to the testing prior to receiving their diagnosis in relation, their experience during the diagnosis, what their experience of any follow up that occurred and their overall experience. 966 patients were ascertained as being diagnosed with a genetic muscle disorder on the point prevalence date. 803 were able to be contacted. 501 adults (>16 years) and parents of 83 affected children as well 178 significant others (spouses, close friends or family) completed the assessment of the questionnaire. 55% of the total cohort of 966 patients had a molecular test result confirming their diagnosis. The experiences of this large cohort of patients diagnosed with genetic muscle disorders and the factors which influence that experience will be described.

http://dx.doi.org/10.1016/j.nmd.2018.06.337

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Audit of impact of the quality of the pre-test information on the outcome of muscle biopsy assessment

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One of the quotidian activities of the pathologist is to rue incompletely filled out request forms. This is of particular concern in the field of muscle pathology where the integration of clinical information with the biopsy results is integral. Anecdotally, it is believed that the quality of the clinical information provided affects the subsequent neuropathological opinion and ultimately the clinical utility of performing a muscle biopsy. We therefore conducted a study to examine the quality of the clinical information provided, and to assess the impact of the pre-test information provided on the pathological opinion. The aim of this was to improve our current referral system and to direct education to the worst offenders. Muscle biopsies performed at a regional neuromuscular unit during 2012 and 2016 were identified through review of the hospital pathology database. A total of 190 cases were identified; of which 135 were identified as eligible (135 from 2012; 55 from 2016). Data collection points and a collection sheet were agreed prior to the study. Each muscle biopsy referral and result was examined and an overall score calculated. Twenty-five per cent of requestors failed to utilise the departmental muscle biopsy request form. The majority of referrers failed to provide basic information on patient's symptoms. Information in relation to muscle atrophy, weakness and myalgia was absent in 80%, 50% and 70% of referrals respectively. The anatomical distribution of symptoms was not apparent in 33-40% of requests. The presence or absence of a family history of neuromuscular disease was included in only 23%. The inclusion of relevant investigation findings was also poor with a creatine kinase level provided in only 56%, while the results of neurophysiology were provided in 52%. The overall scores were poor: 9.33/21 in 2012 and 10.25 in 2016. Rheumatologists and neurologists achieved the highest overall scores. Neuromuscular specialists did not perform significantly better. The lack of clinical information was also found to impair the subsequent pathological opinion. In summary, our study confirmed our neuropathologist's belief that requests for muscle biopsy more often than not lack the necessary clinical information required for assessment. Specialists performed only slightly better than non-specialists but still omitted key clinical information.

http://dx.doi.org/10.1016/j.nmd.2018.06.338

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Clinicopathological study for ultrasound-guided biopsy cases using linear probe

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Muscle ultrasound is a non-invasive technique to detect neuromuscular disorders. Large myopathological findings including fibrosis, fatty infiltration, and inflammation increase muscle echo intensity, which can be used to delineate normal from diseased muscle. But, the association between ultrasound findings and myopathological findings such as nemaline rods, ragged red fibers, and rimmed vacuoles are not clarified. Linear transducer can describe small size findings more easily than convex or sector transducers, so we can detect these small size findings. In this study, we aimed to describe the association between myopathological findings and ultrasound imaging produced by linear transducers. We examined 45 consecutive cases with ultrasound images and muscle pathology findings. Their biopsy sites were selected by MMT scores and muscle CT/MRI findings. Ultrasound examinations were performed by using SSA-640A ultrasound imaging system (Toshiba, Tokyo, Japan) with 15MHz linear transducer. Ultrasound images were evaluated by Heckmatt score. After their ultrasound examinations, we performed open muscle biopsies assisted by ultrasound findings. Each pathological finding described by hematoxylin and eosin and modified Gomori stainings was classified in four categories; none, mild moderate, severe. Patients with Heckmatt score 1 images had almost normal findings. Mild endomysial fibrosis, fiber size variation, endomysial lymphocyte infiltration, cytoplasmic structures including nemaline rods, ragged red fibers, and rimmed vacuoles were scattered in 70% of patients with score 2 images. Perimysial fibrosis and fatty tissue were observed in 50% of score 3 patients. 70 % of patients with score 4 images had severe fatty tissue and grouped atrophy. Lymphocyte infiltrations decreased in score 4 cases. In addidion, score 4 cases with inflammatory myopathies show same severities of fibrosis and fatty tissues as score 2 and 3 cases, and less frequently than score 4 cases of previous report ($p<0.01$). Linear transducer could detect smaller myopathological findings.

http://dx.doi.org/10.1016/j.nmd.2018.06.339

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Skeletal muscle NMR image automatic segmentation using convolutional neural network

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Skeletal muscle manual segmentation remains the bottleneck limiting the more systematic use of quantitative NMR imaging in neuromuscular patients. Muscle automatic segmentation software which has been proposed so far has not provided with adequate solutions. Deep convolutional neural network (CNN) segmentation techniques are revolutionizing the field of image processing. Among advantages, they do not require any prior selection of features, i.e. explicit descriptors of local image information, nor any explicit anatomical model. In this work, our purpose was to take advantage of the extensive learning capabilities of CNN and apply them to segment muscle groups in NMR images. To this end, we used lower limb Dixon out-of-phase scans (148 volumes of thighs and 161 volumes of legs) of patients with different neuromuscular diseases and various levels of fatty infiltration. Thigh and leg muscles (quadriceps, hamstring, triceps surae, foot extensors and fibularis group) were first segmented manually and then used in the training and validation processes of the CNN. After the training period, the segmentation of one volume of 64 slices took less than 2s. The degree of agreement between manual and automatic CNN segmentations was evaluated with the Dice coefficient, which expresses the fraction (0 to 1) of all voxels targeted by the two methods that are identical. It was particularly high for the quadriceps, 0.97. The mean Dice coefficient for all muscle groups was 0.9, demonstrating the effectiveness of the technique in automatically segmenting both healthy and pathological muscle groups. CNN segmentation performance was only minimally degraded in fatty infiltrated muscles. Similarly as in many other image processing applications, CNN offers superior performance for automatic skeletal muscle segmentation, even at this preliminary phase of exploitation, with further significant improvement to be expected with bigger training sets and more advanced software implementation.

http://dx.doi.org/10.1016/j.nmd.2018.06.340

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A novel, ultrafast and robust NMR imaging approach to evaluate disease activity and chronic degenerative changes in skeletal muscle using an optimal fingerprinting radial sequence

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Quantitative water T1 ($T1H_2O$) mapping has been extensively validated to monitor inflammation, necrosis or fibrosis in myocardial tissues and might represent an efficient alternative to water T2 maps for neuromuscular diseases (NMDs) too. However, in presence of fatty infiltrated skeletal muscles, a "global" T1 value would mainly reflect the intramuscular fat content. To avoid this, we proposed here a novel sequence, inspired by the MR fingerprinting (MRF) method, allowing simultaneous estimation of $T1H_2O$ and fat fraction (FF) in the skeletal muscles. The MRF sequence for T1 mapping with water and fat separation (MRF-T1-WF) consisted in the acquisition of a 1400 radial spokes FLASH echo train, with golden angle sampling scheme, following non-selective inversion. The echo time, repetition time and prescribed flip angle were varied throughout the acquisition. For each slice, 175 images were reconstructed using view sharing and a compressed sensing algorithm. A dictionary of 69888 normalized signal evolution curves with

various $T1H_2O$, transmit field efficacy B1 and off resonance frequency Δf values. Each entry in the dictionary contained a pure water and a pure fat signal evolution. For each voxel, the optimal triplet ($T1H_2O$, Δf and B1) and the amplitudes of water and fat signals (w and f) were determined. Acquisitions were performed on a phantom containing different vials at different $T1H_2O$ and FF, on a healthy volunteer and patients suffering from different NMDs (2 Becker muscular dystrophy: BMD, 2 sporadic inclusion myopathy: IBM and 1 Duchenne muscular dystrophy: DMD). Gold standard $T1H_2O$ was measured by spectroscopy and FF was also quantified using the 3pt-Dixon method. On phantom, $T1H_2O$ and FF values estimated with MRF-T1-WF were highly correlated with the spectroscopic $T1H_2O$ and 3pt-Dixon FF ($R2 = 0.96$ and $R2 = 0.98$ respectively, $p<0.05$). $T1H_2O$ and FF maps were obtained on the healthy volunteer and patients at the thigh level. MRF-T1-WF FF values correlated with 3pt-Dixon FF ($R2 = 0.98$, $p<0.05$). The IBM patients exhibited increased $T1H_2O$ values corresponding to the inflammatory processes occurring during this pathology. The MRF-T1-WF sequence measures simultaneously $T1H_2O$ and FF and represents a fast, robust, motion insensitive alternative to standard evaluation of disease activity and chronic degenerative changes in diseased skeletal muscles.

http://dx.doi.org/10.1016/j.nmd.2018.06.341

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Muscle biopsy in the study of muscle disease in pediatric population

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Despite the great advance in molecular genetics, the histopathological evaluation of muscle remains an essential element in the diagnostic study of muscle diseases. The precise clinical selection of the patients, the obtaining of adequate samples for histopathological analysis and the correct use of histochemical and immunohistochemical techniques are considered essential for the adequate performance of the muscular histopathological study. In order to evaluate the usefulness of the muscle histopathological study in children, a descriptive, retrospective study of muscle biopsies performed at the Clinical Hospital of the Pontifical Catholic University of Chile was carried out. All biopsies performed between January 2001 and December 2016, under 18 years were included. Clinical records, procedure protocol and pathology report were reviewed. Results: A total of 240 biopsies were reviewed, average age at the time of biopsy 6.4 years (3 weeks-18 years). The biopsy was abnormal in 73.6%, normal in 25.3% and insufficient or inadequate for analysis in 1.1%. The clinical signs most frequently associated with abnormal biopsy were lack of strength (80.7%), hypotonia (67.7%) and impaired gait (67.7). The most frequent histopathological diagnoses were nonspecific myopathic alterations (28.4%), congenital myopathies (20.9%), dystrophy-dystrophin (-) (19.4%) and dystrophy-dystrophin (+) (9%). The results obtained show that the muscle histopathological study was useful in a high percentage, the sample used for the study was adequate in the majority of the cases and the classical clinical symptoms associated with muscular disease were associated with greater utility of histopathological study.

http://dx.doi.org/10.1016/j.nmd.2018.06.342

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HyperCKemia asymptomatic or oligosymptomatic in an Argentinian neuropediatric cohort

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The diagnosis and follow up of the hyperCKemia in almost all the cases remains a challenge because sometimes they need very invasive studies to finally get into it. To describe patients with hyperckemia and their difference diagnosis. Patients with CK level 1.5 times (at least 2 measurements). We follow up mean to two years. Patients with asymptomatics and oligosymptomatics clinical features. We excluded non neuromuscular disorders (thyroid, celiac disease and pharmacological or drugs). We studied all the patients with muscular dystrophy, electromyography, intermediate metabolism, acid alpha glucosidase, genetics test for McArdle desorder, muscle MRI, muscle biopsy and NGS panel. We review 52 medical charts, 50% were male, with a range age between 2 and 28 years. Only 15 patients remains without a diagnosis. We have 23 muscular dystrophy (18 dystrophnopathy, 2 myotonic dystrophy type 1, 1 beta 1 sarcoglycan, 1 dysherlinopathy and 1 non specific), 12 metabolic (5 CPT II, 4 organic acidurias, 1 Mc Ardle disease, 1 mitochondria disease and 1 glycogenesis type 3), others: 1 RYR-1 and 1 anoctamin. The most frequent diagnosis were the muscular dystrophy and the metabolic disorders. The new implementation of the NGS allows us to rise the accurate diagnosis.

http://dx.doi.org/10.1016/j.nmd.2018.06.343

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ICD code refinement for Duchenne/Becker muscular dystrophy

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The International classification of diseases (ICD) is the foundation for the identification of health trends and statistics, and the international standard for reporting diseases and health conditions. Owned, developed and published by the world health organization (WHO), it is the diagnostic classification standard used for clinical and research purposes. Uses of the ICD codes also include retrieval and analysis of health information for evidence-based decision making; monitoring of the incidence and prevalence of diseases; observing reimbursements trends; and tracking of longitudinal outcomes and adherence to care guidelines. The lack of an ICD code specific to Duchenne has proven a barrier to diagnosis, care, surveillance, research, and access. Previously, Duchenne muscular dystrophy has been classified among a broad category of diagnoses in the standard ICD. In 2016, PPMD led an effort along with The Duchenne Registry (formerly DuchenneConnect), leading clinical and scientific experts, international advocacy partners and the FSH Society to develop a proposal to the ICD-10 Coordination and Maintenance Committee that would expand an existing ICD code (G71.0) to identify Duchenne and Becker muscular dystrophies and Facioscapulohumeral muscular dystrophy (FSHD). A formal nomination and presentation was made by PPMD - in collaboration with the FSH Society - in September of 2017 to the ICD-10 Coordination and Maintenance Committee. In January 2018, we were notified that the proposed codes for Duchenne/Becker and FSHD had been accepted for CMS coding amendment beginning in FY 2019 on October 1, 2018.

http://dx.doi.org/10.1016/j.nmd.2018.06.344

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Treatment responsive outcome measures in mouse models of neuromuscular disease

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Preclinical efficacy evaluations in mouse models of neuromuscular diseases are critical first steps for ensuring the success of therapeutic interventions in human clinical trials. Regulatory agencies such as the US FDA and EMA require robust and reliable preclinical data if animal models exist. We have tested 63 interventions (e.g. small molecules, biologics, exon-skipping and gene therapy) in mdx mice over the last 4 years. These preclinical studies were conducted with more than 2,600 mice, using a well characterized set of outcome measures; body weight and tissue weights, functional measures (grip

strength, *in vitro* force contractions, treadmill exhaustion, voluntary wheel running, echocardiography, plethysmography), histological analyses (inflammation, central nucleation, degeneration, regeneration, fibrosis), serum CK, immunofluorescence and western blot for dystrophin expression. We used TREAT-NMD preclinical standard operating procedures for all applicable outcomes and each study was performed using appropriate blinding, randomization and statistical analysis. Treatment periods ranged from 2 weeks to 9 months depending on the nature of the intervention with an average sample size per group of n=14, and an average of 9 outcomes tested, yielding over a quarter million data points. Of the 63 interventions, only 32% showed statistically significant efficacy in 2 or more of the outcomes, indicating that 68% failed to show efficacy. Echocardiography, exhaustion assay, *in vitro* force contractions, western blot and immunofluorescence were consistently responsive to the efficacious interventions. Parameters such as histological measures, serum CK and voluntary wheel failed to show improvements in studies where other outcomes detected efficacy. Failure of some therapeutic interventions could be attributed to questionable therapeutic targets. Our data suggests that careful selection of appropriate endpoints is essential for all preclinical mouse efficacy trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.345

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Development of a microRNA-155 inhibitor as a therapeutic for neuroinflammatory and neurodegenerative diseases

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Our objective is to develop a multi-pathway therapeutic approach to the treatment of neurodegenerative diseases like ALS and spinal cord injury (SCI). A major contributor to the pathology of neurogenerative conditions is the excessive inflammation in the CNS, mediated by T lymphocytes, M1-type macrophages and microglia. This has been associated with tissue destruction, neuroaxonal injury and inhibition of axon regeneration. miR-155 is a pro-inflammatory microRNA highly upregulated in activated immune cells, where it mediates cell proliferation and survival, and drives the inflammatory response. In the CNS, miR-155 is expressed in activated microglia, astrocytes and neurons and genetic ablation of miR-155 improves repair and recovery in mouse models of ALS, MS/EAE and spinal cord injury. miRagen Therapeutics, Inc. has developed oligonucleotide inhibitors of miR-155 (antimiR-155). When administered to stimulated, primary human immune cells, antimiR-155 reduces the activation and proliferation of T helper cell subsets 1 and 17 as well as moDCs and reduces the secretion of pro-inflammatory cytokines. Further, kinetics and characteristics of immune cell infiltration, neuronal degeneration and miR-155 expression were evaluated in mouse models of ALS and contusion SCI. In the latter, intravenous administrations of antimiR-155 increased locomotor recovery and autonomic functions and significantly reduced neuroaxonal degeneration. Further, significant reduction in fibrosis in the soft tissue surrounding the site of injury was seen, which is known to aggravate axonal regeneration. Efficient uptake of antimiR-155 by cells in the CNS was demonstrated. These data support the development of antimiR-155 as therapeutic for neurodegenerative diseases, as miR-155 inhibition decreases the activation state of disease-relevant immune cell subsets and improves neuronal function.

http://dx.doi.org/10.1016/j.nmd.2018.06.346

DUCHENNE MUSCULAR DYSTROPHY - PHYSIOTHERAPY

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Minimal detectable change in the North Star ambulatory assessment (NSAA) in Duchenne muscular dystrophy (DMD)

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The NSAA is a validated functional scale for ambulant boys with DMD used in natural history studies and clinical trials. An important consideration for outcome measures is the magnitude of change that is clinically meaningful. In the present study we used longitudinal analysis of natural history data to identify minimal changes in NSAA scores that can be attributed to DMD disease progression, i.e., to persistent and irreversible changes, rather than measurement variability. We analyzed boys with DMD aged 5-15 years at first assessment in the UK North Star Network database. Minimal detectable changes were estimated based on longitudinal mixed effects models for each boy's trajectory of function over time. Trajectories were modeled to allow for periods of both improving and declining function with age. Based on the variation around these patient-specific trajectories, a threshold for NSAA score change was calculated such that declines exceeding that threshold provide >80% confidence that the patient experienced a true decline in function. Distribution-based estimates of clinically important differences were also calculated as 0.5 standard deviations (SD) overall and by age group. NSAA assessments from 1826 clinic visits among 302 patients were analyzed. Median follow-up was over 1 year and fitted models explained >95% of the variability in NSAA scores. Thresholds corresponding to >80% confidence in disease progression were 3.1 for the NSAA total score and 7.5 for the linearized scores, and were smaller than estimates based on 0.5 SD. Thresholds for detectable change in NSAA scores can be useful for informing endpoint definitions and interpreting drug effects in clinical trials, and warrant confirmation in other natural history studies and complementary analyses with additional clinical measures.

http://dx.doi.org/10.1016/j.nmd.2018.06.347

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Prognostic factors for changes in 4-stair climb ability in patients with Duchenne muscular dystrophy

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The timed 4-stair climb (4SC) is used to assess ambulatory function in patients with DMD and as an endpoint in clinical trials. This study identified prognostic factors for changes in 4SC velocity, developed a composite prognostic score, assessed consistency across data sources and quantified impacts on trial sample size and power. Boys with DMD receiving care at UZ Leuven in Belgium, Cincinnati Children's Hospital and Medical Center (CCHMC), or those who received placebo in the phase 3 DMD trial of tadalafil, were studied. Annualized change in 4SC velocity was studied over ~1-year intervals (8-16 months follow-up; required to have 4SC < 12 seconds at baseline) and related to candidate prognostic factors using multivariable regression. Simulations were used to quantify impacts on trial design. Mean (SD) changes from baseline in 4SC velocity in Leuven, CCHMC and the tadalafil trial placebo arm were -0.06 (0.65), -0.12 (0.56) and -0.18 (0.41) stairs/second (n=235, 543 and 82), respectively. Prognostic models incorporating baseline age, 4SC and duration of steroid use explained only a small portion of variability in 4SC outcomes (R-squared: 8% to 17%). Adding baseline walking and rising ability significantly increased explained variation (R-squared: 29% to 36%). In a randomized trial with equal allocation to treatment and placebo arms, baseline adjustment for such a prognostic score would enable a treatment effect of 0.25 stairs/second to be detected with 100-120 total patients, compared to 170-190 patients without use of the prognostic score (at 80% power). Combining multiple measures of ambulatory function more than doubled prognostic accuracy for 1-year changes in 4SC velocity. This finding was consistent across data sources, and with previous studies of prognostic factors for change in 6-minute walk distance in DMD. Clinical trials incor-

porating a validated prognostic score could reduce sample size requirements by approximately 40%.

http://dx.doi.org/10.1016/j.nmd.2018.06.348

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Home based movement monitoring allows pivotal trials in DMD with ten times less patients than classical outcomes measures

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Currently used primary outcomes in Duchenne muscular dystrophy require sample size group between 100-150 patients per treatment group to capture a stabilization over a one year period. Given the failure of several programs based on a 1 year long pivotal trial, a general trend in the phase 3 trial is to move to trial duration up to 24 months. This decreases the number of patients available for conducting phase 3 trials, and increases the duration of exposure to placebo or to a drug that does not work. There is thus a need for more sensitive, precise outcome, with better size effects. We have been developing for several years an holter of movement, ActiMyo®, that captures any single upper or lower limb movement, using magneto inertial technology. In lower limb, ActiMyo® captures every stride and computes its length and its speed. We pooled all data captures in 45 ambulant DMD patients and 45 aged matched healthy controls and reviewed baseline and longitudinal evolution in steroids treated patients. The most sensitive measure is the top velocity (95th percentile) of strides computed during a 180 hours recording period. The measure is highly discriminant between patients and controls, and correlates with 6MWT, NSAA and four stairs climbing test in patients. The minimal clinically relevant change is 0.1m/s, which corresponds to 36 m at the maximal speed during 6 minutes. Interestingly, the variation in the overall DMD patients over a 6 month period is -6.8% (Standard deviation 8.3 %), and on a 1 year period -13.8 % (SD 10.4). The effect size is even more interesting in patients walking between 300 and 450 m at the 6 MWT, with a delta of -15.6 % and a SD of 7.9%. In comparison with the 30 m delta and standard deviation of 80 m for the 6MWT, this technology allows to demonstrate a significant drug effect using 10 times smaller patient groups. This outcome is currently under qualification process by the European Medical Agency.

http://dx.doi.org/10.1016/j.nmd.2018.06.349

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Genetic association study of articular range of motion in the CINRG Duchenne natural history study

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Joint contracture severity in DMD is variable between patients with comparable muscle weakness. We planned a genetic association study of contracture severity in participants in the CINRG Duchenne natural history study. We selected 109 participants of European American ancestry for genotyping with the illumina exome chip, in order to minimize population stratification bias. SNPs with minor allele frequency >0.05 were included in the analyses. Range of motion (ROM) was assessed using a standard goniometer. Prevalent DMD contractures were measured on the dominant side: elbow extension (n=104), wrist extension (n=104), knee extension (n=62), and ankle dorsiflexion (n=61). A linear model of association between articular ROM and genotype was used, with brooke upper extremity score and vignos lower extremity score as covariates, to adjust for muscle weakness in upper or lower limbs as relevant. QQ plots were visualized in order to control for type I or II error inflation. A bonferroni correction for 27,025 SNPs with MAF>0.05 was applied, leading to "exome-wide" significance of P=1.85*10-6. A more permissive "suggestive" threshold of P=10-4 was also considered. The only exome-wide significant association signal (P=1.36*10-7) was observed using an autosomal dominant inheritance model for rs12506517 (70kb upstream BANK1, encoding a B-cell-specific scaffold protein that mobilizes Ca^{++} from intracellular stores). This protein promotes Lyn-mediated tyrosine phosphorylation of inositol 1,4,5-trisphosphate (IP3) receptors. Several "suggestive" signals were observed, including SNPs in *FAM26F* (Ca^{++} homeostasis regulator), *DST*, *DYSF*, and *LTBP4*. This study suggests a role of SNPs in Ca^{++} homeostasis genes and other genes in predisposing DMD patients to early contractures. Further studies are needed to validate these associations and elucidate their mechanistic underpinnings, before these genes and the corresponding proteins can be considered as biomarkers or therapeutic targets.

http://dx.doi.org/10.1016/j.nmd.2018.06.350

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Development of a conversion method to enable an accurate PUL v.2 score from PUL v.1.2 data in a cohort of Duchenne muscular dystrophy patients

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Outcome measures in neuromuscular disorders are constantly being reviewed and updated to ensure accurate and relevant clinically meaningful information is being collected. The data collected allows detailed, appropriate clinical input, plus analysis of disease progression. The performance of upper limb (PUL) scale has been developed and established for the use in ambulant and non-ambulant DMD patients. It is currently the most commonly used outcome measure that captures upper limb function in Duchenne muscular dystrophy (DMD). Following psychometric and clinical analysis of the PUL v1.2 an improved version was created, PUL v2.0. There are noticeable differences between the two versions, including number of items on the scale and scoring system. Although PUL v2.0 is currently being used in a number of global trials, data in recent natural history studies has been collected using the PUL v1.2 scale. It is therefore desirable to have information on how the 2 scales compare. We present a proposed scoring conversion method. This method was developed by critically and clinically analysing all items on both versions, individually. Using clinical reasoning and knowledge of the disease, the PUL v1.2 items were rescored using the PUL v2.0 scoring system. Using PUL v1.2 data from the AFM dataset, longitudinal data collected for 95 patients in 5 international sites over 3 years was analysed with the proposed new scoring method. We will explore the relationship between PUL v1.2 and PUL v2.0 to ensure there is a smooth monotonic relationship between the 2 scores. Furthermore we will describe and correlate longitudinal changes for the 2 scores (e.g. 1 year changes for 75 boys) and explore trajectories over time for non-ambulant boys. A separate dataset of 130 DMD boys, scored simultaneously with PUL v1.2 and v2.0 will be used to cross-validate the proposed scoring conversion. We will similarly describe the relationship between the 2 scores. The analysis is ongoing; results will be presented at the conference.

http://dx.doi.org/10.1016/j.nmd.2018.06.351

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Relationship of lower extremity strength and range of motion on timed function tests in Duchenne muscular dystrophy

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Current therapies in Duchenne muscular dystrophy (DMD) include contracture management and glucocorticosteroids (GC) with timed tests being used to monitor progression and predict loss of ambulation. The objective is to understand the role of GC on contracture, progression and interplay between strength and contractures on timed velocity tests. Individuals were enrolled in the CINRG Duchenne natural history study at 20 sites obtained in a standardized manner. Data included: range of motion (ROM) in 4 joints (elbow (EE) and wrist (WE) extension, knee extension (KE) and ankle dorsiflexion(DF), timed tests (supine to stand, stairs, 10MWT), quantitative muscle testing (QMT) of knee flexors and extensors. We assessed EE and ankle DF ROM across the age span and over time. Longitudinal mixed effects models assessed the relationship between strength and ROM on velocity with age and GC status as covariates. We enrolled 440 individuals; mean baseline age was 10.7 +/-5.7 and 15.3 +/-6.6 at last study visit. At baseline, 292 were ambulatory; 192 at last study visit. Only 16% were GC naïve, 81% of cohort ranged from 6mos- 25 years on GCs. GCs have initial affect on ROM compared to steroid naïve and no significant effect on progression. QMT, ROM, age and GCs contribute to timed tests. KE strength and DF ROM are significant predictors of velocity for all timed function tests ($p<.001$). KE strength is the primary predictor of walking velocity estimating that every pound increase in KE results in a 0.042 m/s improvement in 10MWT and a smaller similar increase of .009m/s with every degree of ankle DF ROM. GC use provides an improvement in strength and ROM but does not affect rate of change. Knee strength have a greater influence on speed of timed tests than DF ROM although both are statistically significant predictors of velocity. Results show that retaining knee strength, along with management of contractures, are important to maintain the ability to run, climb, and stand.

http://dx.doi.org/10.1016/j.nmd.2018.06.352

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Disease progression in arm versus leg muscles in Duchenne muscular dystrophy

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Leg muscles have been extensively studied using magnetic resonance imaging (MRI) and spectroscopy (MRS) in Duchenne muscular dystrophy (DMD). Research in the arm muscles is rapidly advancing, however, the progression of MRI/MRS measures in the arms and legs of the same individual has not been documented. 88 corticosteroid-treated boys with DMD (24 non-ambulatory) and 28 controls aged 5-18 years participated in this cross-sectional multi-center study. Subjects participated in two MR sessions, each lasting 45 to 60 minutes. Multi-echo 2D spin echo MRI sequences were used to generate T2 maps for the shoulder, upper arm, forearm, thigh, and calf (TR: 3000 ms; TE: 20 ms to 320 ms), and regions of interest were manually defined. Single voxel 1H MRS (TR: 9000 ms and TE: 11, 27, 54, and 243 ms) was used to calculate fat fraction (FF) in the deltoid (DEL), biceps brachii (BB), vastus lateralis (VL), and soleus (SOL). Proximal muscles of the leg (biceps femoris long head and VL) tended to have the highest MRI T2 and FF values, with slightly lower values in the proximal muscles of the arm (subscapularis, infraspinatus). The forearm muscles, gracilis, tibialis anterior, and tibialis posterior were the least affected muscles. The DEL and upper arm muscles (BB, triceps brachii, and brachialis) had similar T2 and FF values to several muscles of the lower leg (SOL, medial gastrocnemius, and peroneals). While lower T2 and FF values were seen in arm compared with leg muscles, considerably elevated T2 values were seen in proximal arm muscles in boys as young as 5, and FF was elevated in boys as young as 9. Early and progressive involvement of the proximal upper extremity muscles in DMD should be considered in both clinical trial design and treatment of young and older boys with DMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.353

P.306

Utility of the Bayley-III, North Star Ambulatory Assessment, and 100 meter timed test in quantifying gross motor delay in very young boys with Duchenne muscular dystrophy

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Preclinical and early clinical trial data strongly suggest that early treatment has the potential to maximize treatment benefit in children with Duchenne muscular dystrophy (DMD). With the historic average range of diagnosis between the ages of 3-5 years, the magnitude of change in development as a result of disease natural history is not as well defined as in the older cohorts. This study aims to examine the utility of the Bayley-III, NSAA, and 100m for use in the very young DMD cohort, confirm differences in motor performance between young boys with DMD and typically developing peers and document natural history data and reference values in young boys with DMD. Eighty-four boys with a confirmed diagnosis of DMD ages 0.8 - 6.9 years (Mean 4.7 $\pm$ 1.5) were evaluated using the Gross Motor portion of the Bayley Scales of infant and toddler development, third edition (Bayley-III) (N=29, 0.8 - 5.9 years), North Star Ambulatory Assessment (NSAA) (N=62, 2.3 - 6.9 years) and the 100 Meter Timed Test (100m) (N=60, 3.5 - 6.9 years) as standard of care during regularly scheduled clinic visits. Longitudinal data on a sub cohort (N=55) was also collected. Bayley-III gross motor scaled scores were lower in boys with DMD compared to controls (Mean 5.7 $\pm$ 2.1; typical peers 10 $\pm$ 3) across the age span. 100m times were significantly lower than age/size matched peers across the age range (Mean 52.7% of predicted). The delay in gross motor skills remained present in the cohort of subjects with follow-up assessments. Gross motor delay can be measured in infants and young boys with DMD using the Bayley-III, NSAA, and 100m. The Bayley-III can be useful across the age range and has the potential to be useful as a continuous study outcome in a younger DMD cohort. Reference values by age and steroid regimen will be presented to document the natural history.

http://dx.doi.org/10.1016/j.nmd.2018.06.354

P.307

Relationships between hand strength and function in non-ambulant patients with Duchenne muscular dystrophy or spinal muscular atrophy

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The objective of this work was to establish the relationships between hand strength and function in non-ambulant patients with Duchenne Muscular Dystrophy (DMD) or Spinal Muscular Atrophy (SMA). The maximal handgrip and key pinch strength was measured with the MyoGrip and MyoPinch dynamometers, respectively. Hand function was assessed by the Motor Function Measure items for distal upper limb (MFM D3 UL) and by the Cochin scale. Fifty-three DMD and 23 SMA patients (age 8–31 years) were included. The scores to the functional scales and their items were significantly correlated to strength ($P<0.001$). However, the Spearman correlation coefficients between the items scores and muscle strength varied between 0.783 and 0.262, suggesting that some functional items require strength more than others. Hand function was rather preserved when handgrip strength and key pinch strength were higher than ~8 kg and 3.4 kg, respectively. For lower strengths, hand function scores decreased with decreasing strength although a large inter-individual variability was observed. For all the functional items but one, the strength corresponding to the "no disability" score was significantly higher than the strength associated to the "greatest disability" score. The strengths corresponding to the intermediate scores were not al-

ways significantly different from each other. At equivalent strength deficit, DMD and SMA patients similarly performed most of the items of the functional scales. A few items however were better realized by SMA patients, probably because they developed less contractures. Hand function depends on strength but is far from being the only variable required to perform motor tasks correctly. The large variability in the relationships prevents prediction of the functional consequences of a strength modification, possibly because of the contribution of contractures, motor compensations and psychological state.

http://dx.doi.org/10.1016/j.nmd.2018.06.355

P.308

Determination of the minimal clinically important difference (MCID) for clinical trial outcome measures in Duchenne muscular dystrophy

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Statistically significant differences in clinical trial outcome measures do not always translate into relevant or meaningful differences for patients and their families. Minimal clinical important difference (MCID) is defined as the smallest change that is considered meaningful by patients, parents and/or clinicians. It can be determined using statistical or qualitative methods or often a combination of the two. As therapeutic advances in the treatment of Duchenne muscular dystrophy (DMD) progress, there is a pressing need to determine the MCID for Clinical trial endpoints. This study aims to determine the MCID for two commonly functional rating scales used as clinical endpoints in DMD: the North Star Ambulatory Assessment (NSAA, 34 points) and the performance of upper limb (PUL, 74 points). This cross sectional, multi-site study will use a single time point administration of a specifically developed questionnaire exploring patients', their families' and clinician's views on the MCID for NSAA and PUL. The questionnaire includes 6 questions: 3 related to natural disease progression and 3 pertaining to participation in clinical trials. The study will include up to 100 patients (7-18years) and their families and 20 clinicians with neuromuscular experience. The MCID will be established as the smallest change for the majority of participants. Concordance between patients/parents and clinician responses in the questionnaires will also be explored. Preliminary NSAA results so far indicate that a meaningful change for parents would be: preventing the loss of one activity (5/8) and preventing the deterioration in at least 2 activities (5/8). For all parents, the minimum requirements for participation in a clinical trial was slowing down a possible decline in motor function rather than improving it or completely stopping any decline. This on-going study will aid in the design and interpretation of the results of DMD current and future trials. It would be valuable not only for patients, families and advocacy groups but also for clinicians and regulatory authorities.

http://dx.doi.org/10.1016/j.nmd.2018.06.356

P.309

The effects of trunk and lower extremity flexibility on lumbar lordosis in children with Duchenne muscular dystrophy

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The aim of this study was to investigate the effects of lower extremity and trunk flexibility on lumbal lordosis in children with Duchenne muscular dystrophy. Thirty children with DMD were included in the study. Functional levels of children were determined by Brooke lower extremity functional classification (BLEFC). Flexibility of lumbal extensors and hamstrings, tensor fascia latae, hip flexors, and gastrocnemius muscles were evaluated. Lumbar lordosis was measured by flexible ruler. The mean age of children was 5±2.03 years. Nineteen (63.33%) children were in Level 1 and 11 (36.67%) in Level 2 according to BLEFC. The mean flexibility scores of lumbal extensors were 0.88±6.97 cm, hamstrings 60±30°, tensor fascia latae 18.33±4.64°, hip flexors 27±18.24 cm, and gastrocnemius muscles were 81.8±10.88°. There was a moderate, positive correlation between hamstring flexibility and lumbar lordosis ($r=0.458$, $p<0.05$). In our study, the hamstring flexibility was found to have an important effect on the lumbar lordosis in DMD in the early period when compared to other lower extremity muscles' flexibility. Hamstring flexibility should be increased/maintaned in children with DMD from early period of the disease to control lumbar lordosis.

http://dx.doi.org/10.1016/j.nmd.2018.06.357

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The comparison of children with Duchenne muscular dystrophy and healthy peers in terms of pulmonary and upper extremity functions

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Although it is known that the pulmonary and upper extremity functions are affected in later stage of Duchenne muscular dystrophy (DMD) negatively, we do not have a clue about the early stages of the disease. The aim of this study was to investigate the differences in pulmonary and upper extremity functions between children with DMD in early stage and healthy peers. A total of 26 children consist of 13 with DMD in Level I according to Brooke Upper and Lower Extremity functional classification Systems and 13 healthy peers were included in the study. After recording demographic characteristics, the pulmonary function (forced vital capacity and forced expiratory volume at 1 second) was assessed by Pulmonary function Test (PFT), and upper extremity functions by the performance of upper limb (PUL). The comparison of test results were analyzed by Mann-Whitney-U test. The mean age of children with DMD and health peers were 88.37±5.20 and 80.06±2.85 months, respectively. No difference was found between children with DMD and healthy peers with regard to demographic characteristics ($p>0.05$). The pulmonary and upper extremity functions of healthy peers was found to be higher than DMD subjects who were in the early stage ($p<0.05$). Our study showed the negative influence of disease on pulmonary and upper extremity functions in children with DMD from the early stages of the disease process.

http://dx.doi.org/10.1016/j.nmd.2018.06.358

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The effect of kinesiologic taping on balance in Duchenne muscular dystrophy

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It is known that there is a relationship between balance and motor function in Duchenne muscular dystrophy (DMD). The aim of this study was to investigate acute effect of kinesiologic taping on balance in DMD. Thirty-three children with DMD who were in Level 1 and 2 according to the Brooke lower extremity functional classification (BLEFC) were included in this study. Balance of the children was assessed by timed up and go test (TUGT) and functional reach test (FRT) which are reliable for DMD. Then, kinesiologic taping with facilitation technique was applied bilaterally on quadriceps femoris and tibialis anterior muscles. Assessments were repeated 1 hour after taping. Comparison of the assessments were performed by Wilcoxon signed rank test. The mean age of children was 98.61±23.88 months. Fourteen children were classified as Level 1 and 19 as Level 2 according to BLEFC. It was found that time of TUGT decreased ($p=0.006$), and distances of forward ($p=0.001$), right ($p=0.000$) and left ($p=0.003$) reach increased after taping. Our study showed that increase of balance by taping in DMD can affect the children's function, positively. Therefore, kine-

siologic taping may be included in treatment programs of DMD in early stage.

http://dx.doi.org/10.1016/j.nmd.2018.06.359

P.312

Factors influencing spontaneous maximal stride speed in individual Duchenne muscular dystrophy boys

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The objective is to increase the homogeneity of the ActiMyo® home recording data in DMD clinical trials without impacting recording duration and patient compliance. ActiMyo® permits home based gait analysis in an uncontrolled environment and is currently in the qualification process as an outcome measure in the EMA. The optimal cumulative recording duration to achieve the monitoring of drug efficacy during a clinical trial is up to 180 hours, as variability of recording during this period of time is below 5%. The 95th percentile of stride velocity (95th PSV) is the most sensitive to change variable, and has the potential to considerably decrease the number of patients required to run a phase 3 clinical trial. Factors influencing this parameter, like day of the week, time of the day and patients' compliance are still unknown. We reviewed our baseline data in ambulant DMD patients using an ActiMyo® to better understand the influence of timing of the day (N=45), day of the week (N=10) and compliance (N=28) on the 95th PSV. The 95th PSV for the entire day is 1.582 m/s with a standard deviation (SD) of 0.378 m/s. No significant difference between morning (mean 1.564 m/s and SD 0.384 m/s) and afternoon (mean 1.600 m/s and SD 0.387 m/s) recording periods is detectable. Averaged on 180 hours of recording we obtained a compliance rate of 90%. A statistically significant variation of 0.0218 (mean -7.34% and SD 9.19%) exists between the weekend and the average over weekdays, since patients walk less and more slowly during the weekend. We found no correlation between patients' compliance (number of hours during which the ActiMyo® is worn) and the 95th PSV. Only weekend days versus weekdays have the potential to significantly influence individual patients' maximal stride speed. Although this fluctuation remains far below classically accepted 15% variability in outcomes like 4SCT and 6MWT, we recommend a constant use of ActiMyo® through the week.

http://dx.doi.org/10.1016/j.nmd.2018.06.360

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Use of a powered arm support devices for upper limb function in non-ambulatory men with Duchenne muscular dystrophy

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Our project is exploring the benefits of powered arm support devices (PASDs) in non-ambulatory young men with DMD, using the Ayura Actively Actuated Device and the JAECO WREX as our exemplars. The WREX is a basic mechanical arm support device; the Ayura is an Actively Actuated Device (AAD), which is new to the powered arm support field. PASDs are in great need of additional research to determine efficacy and suitability in populations with upper limb deficits. Although PADs increase confidence, dignity, the ability to engage in social situations, and independence, there is a significant need for standardization of evaluation methods, along with cost determination and quality of life. Thirty young men with DMD with significant limitations in their upper limb function have been recruited. Monitoring and assessment occurs in their natural environment focusing on UL function and activity engagement through a mobile tracking device, the ActiGraph GT9X. We have included validated UL assessments (Brooke UE Scale, Wolf Motor Function Test) self-report of quality of life, and a newly developed UL ADL Activity Self-Report, along with personal goal achievement (Goal Attainment Scale), and determination of paid/non-paid caregiver time, and cost assessment of paid caregivers. Participants are randomized to basic or AAD, and data are collected at baseline, at the installation of the PASD, the end of the 30-day use of the PASD (while using the device), and post 2 weeks' conclusion of the study (following removal of the device). Caregiver time is logged throughout the study duration (60 days). Data are providing important knowledge and objective results regarding the use of AAD, such as the Ayura, in comparison to basic mechanical arm supports in young men with DMD with limited UL function. The information gleaned from this study is greatly strengthening the argument for these devices to increase independence and lower caregiver time and cost commitments.

http://dx.doi.org/10.1016/j.nmd.2018.06.361

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Kinematic/behavioural fingerprints in Duchenne muscular dystrophy and their clinical applications

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Clinical trials for Duchenne muscular dystrophy (DMD) rely on endpoints of muscle function and strength, which require attendance to hospital appointments. These results can be influenced by patient motivation/performance on the day. Furthermore, many outcome measures such as scales involve human judgement and thereby introduce subjective bias. As a consequence, a larger sample size and longer duration of clinical trials are required to correct for these variables, often delaying access to novel therapies. Due to the slowly progressive nature of the disease, accurate and precise tracking of movement kinematics of clinical assessments and natural activities of daily living would provide an important insight to understand disease progression and response to therapy. Leveraging Artificial Intelligence with wearable body sensor networks, we can now deploy a non-invasive, unobtrusive and wireless system, the "AI suit" which can be easily attached to clothing for the recording of body motion in a natural environment. The sensor data provides us with high-resolution body kinematics and has been studied on a number of healthy volunteers of adult age and on adult subjects affected by Friedreich's Ataxia. In this on-going longitudinal study, we are investigating the 24/7 kinematics of full-body movement behaviour in up to 16 subjects affected by DMD, ambulant and non-ambulant and in 10 healthy age-matched boys, over the course of one year. A comprehensive and continuous data set is integrated from different types of sensors, to derive a digital biomarker of disease state. Using pattern recognition and classification algorithms, we are extracting objective measures of disease progression from patient motor pattern data whilst being assessed in clinic with gold-standard outcomes, and whilst performing activities of daily living "in the wild". The aim of this study is to derive new clinical endpoints that quantitatively capture individual variations in disease progression and variations in movement performance throughout the day. Preliminary results will be presented.

http://dx.doi.org/10.1016/j.nmd.2018.06.362

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Stride to height ratio as a new ambulatory outcome measure in Duchenne muscular dystrophy

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Gait disturbance in Duchenne muscular dystrophy (DMD) is progressive, with significant shortening of stride length up to the point of permanent loss of ambulation. Anthropometric standardization of stride length using standing height (stride:height ratio, SHR) facilitates longitudinal evaluation of this characteristic against the backdrop of childhood growth as well as comparisons with typically-developing children regardless of age. Stride length to height ratio (SHR) was measured to characterize progressive ambulation impairment over time in boys with DMD aged 4-12 years vs. controls at baseline

and 12 months. Clinical assessments included anthropometric measures, six-minute walk test (6MWT) with step counts, timed 10- and 25-meter walk/run tests (10MRW, 25MRW), quantitative isometric knee extension strength and PODCI functional health questionnaires. The SHR in typically-developing controls was 1.08 +/- 0.12 at baseline, with no significant differences at the one-year follow up visit. In boys with DMD, the SHR differed significantly from controls at baseline (SHR 0.74 +/- 0.14, $p<0.0001$), and decreased significantly by an average of 0.08 +/1 0.11 ($p<0.0081$) over one year, exceeding the estimated minimal clinically important difference of -0.046. The SHR showed strong and consistent relationships with 6MWT distance, 10MRW and 25MRW times, weight-adjusted knee extension strength and PODCI Transfer and Basic Mobility subscale scores (adjusted R2 range 0.89 - 0.98). The range of performance for SHR in DMD boys was between 1.0 in mild disease and 0.3 near the loss of ambulation, with a consistent inflection point of 0.60 in all comparative relationships below which physical ability was significantly impaired. Stride to height ratio is a biomarker of DMD progression that is quickly assessed in with minimal equipment and that describes ambulatory ability and risk of significant loss of function.

http://dx.doi.org/10.1016/j.nmd.2018.06.363

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Utility of ACTIVE workspace volume as a clinically meaningful measure of functional capacity in individuals with neuromuscular disease

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ACTIVE, a custom video game, uses a skeletal tracking algorithm to quantify the worskpace volume (WSV) with which a person can interact by reaching and leaning in three dimensions to squish spiders or dig for jewels. ACTIVE evaluates a combination of upper-extremity and proximal muscle function, making it an ideal tool to identify and track impairment across a spectrum of abilities in individuals with neuromuscular disease. This study explored the validity and functional relevance of ACTIVE across a variety of neuromuscular disorders and its ability to measure change as a result of treatment. Three hundred and thirty five individuals with neuromuscular disease including Duchenne muscular dystrophy (n=119), Becker muscular dystrophy (n=41), limb girdle muscular dystrophies (n=113) performed ACTIVE, other traditional assessments of upper extremity and lower extremity function, and self- and parent-reports of function as appropriate at regularly scheduled clinic visits. ACTIVE demonstrated validity by significantly correlating to disease-specific validated outcome measures (Rho= 0.5 - 0.9, $p<0.001$). ACTIVE also reduced the ceiling and floor effects when compared to traditional scales as ACTIVE measures function on a continuous scale. We explored the minimum clinically important difference in ACTIVE score, drew comparisons to patient reports of function for individual activities of daily living (ADL), and formulated minimal WSV requirements for each ADL. Additionally, ACTIVE was responsive to intervention in a sub-cohort of the DMD group that performed ACTIVE pre and post steroid initiation. ACTIVE is able to quantify functional abilities in patients across ages and diagnoses on a single continuous scale and is responsive to intervention in neuromuscular disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.364

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Clinically meaningful change on the 100 meter timed test in neuromuscular diseases

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The 100 meter timed test (100m) is a fixed distance ambulatory assessment used to quantify maximal ambulatory ability in children and adults. The purpose of our study was to establish the minimal clinically important difference (MCID) of the 100m in muscular dystrophies to better interpret results over time and evaluate its utility to predict loss of ambulation (LOA). We collected longitudinal 100m times in cohorts with Duchenne muscular dystrophy (DMD) and limb girdle muscular dystrophies (LGMD) 2E and 2A. The DMD cohort included 149 boys (mean age: 7.7 +/- 2.7 years, range 3.5 to 14.7 years) and LGMD cohort included 45 subjects (mean age: 25.0 +/- 13.6 years, range 2.9 to 55.2 years). All subjects completed the 100m as quickly as possible at one study visit. The time to complete the 100 ranged from 28-217 seconds. A subset (n=90 DMD; n= 28 LGMD) completed the 100m at subsequent visits between 6 months and 2 years after baseline. The MCID for the 100m was calculated as 1/3 the standard deviation of baseline values as well as the standard error of measurement (SEM) approach. The MCID generated for DMD was 8.5 seconds using the most conservative method. Using the MCID 60% of our longitudinal cohort demonstrated a significant decline in ambulation over 12 months. Subgroup analysis of the effect of disease phases, such as young children, ambulatory and transitional ambulatory groups, on MCID will be presented. A 100m time of 100 seconds emerged as a critical value for predicting loss of ambulation in DMD as 75% of the cohort lost ambulation within 1 year when their time to complete 100m increased to over 100 seconds. One hundred percent of the DMD cohort lost walking ability within 1 year (average of 9 months) once their walking time increased over 117 seconds. Differences in the LGMD cohort will be discussed. In conclusion, the 100 meter timed test can be implemented in both pediatric and adult populations and can measure meaningful changes over time.

http://dx.doi.org/10.1016/j.nmd.2018.06.365

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Insights from a multisite study utilizing dedicated technology to assess electrical impedance myography as an outcome measure for Duchenne muscular dystrophy

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Improved methods for assessing disease progression and response to therapy in Duchenne muscular dystrophy (DMD) are greatly needed to improve the speed, sensitivity, and accessibility of clinical trials. One painless, non-invasive, and relatively inexpensive technology that holds promise is electrical impedance myography (EIM). In EIM, a weak, high frequency electrical current is applied across two electrodes and surface voltages are measured with a second set of electrodes overlying a muscle of interest. Alterations in muscle composition and structure change the impedance characteristics of the muscle. A recent study using off-the shelf whole-body bioimpedance equipment indicated the potential of this approach to identify DMD progression. In this 5-site study, we assessed the potential of a Myolex, Inc mView^{TM} system specifically designed for this purpose. 71 boys with DMD ages 8.72±4.18 years and 72 healthy boys ages 8.64±4.10 years were enrolled and followed for up to 1 year. Measurements were made on 7 upper and lower extremity muscles; functional assessments were also completed. EIM identified significant baseline differences for multiple EIM parameters, including resistance at 50 and 100 kHz, which also correlated with functional measures including the 6-minute walk test and the Northstar Ambulatory Assessment. Longitudinal data showed that EIM was highly sensitive to disease progression. Sample size estimations based on these data sets suggest that EIM technology could be used to substantially reduce study size needs in DMD therapeutic trials lasting as short as 6 months. In a subanalysis, we also assessed upper extremity EIM parameters in older and non-ambulatory DMD boys and identified evidence of excellent sensitivity to pro-

gression in this group as well. In summary, EIM data obtained with this dedicated system hold the promise of serving as a useful multipurpose tool for tracking DMD progression and response to therapy in future DMD clinical trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.366

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Can we use elastic bandage in children with Duchenne muscular dystrophy by therapy taping methods? Pilot study

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To assess the effect of elastic bandage by Therapy Taping Method on motor functions in children with Duchenne muscular dystrophy (DMD). Five children, divided in two groups (walked and no-walked) with confirmed clinical diagnosis of DMD that visited the physiotherapy clinic at UniMetrocamp/Wyden were selected. Their degree of motor function was assessed by Motor Function Measure (MFM). After that, they performed physical therapy for two months and were reassessed according to the mentioned scale. We initiated the use of bandage technique in oblique muscles and quadriceps bilaterally in walked group, and in wrist extensor and scalene muscles in non-walked group. The bandages were exchanged weekly, in a total of 24 weeks. The data was analyzed by comparing results before and after the treatment. The scores of the MFM increase after the combination of the use of elastic bandage with physiotherapy. The elastic bandage using the Therapy Taping Method allowed increased execution capacity of the motor activities of these children with DMD. In no-walked group score of the distal function increase and the walked group was standing function.

http://dx.doi.org/10.1016/j.nmd.2018.06.367

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Trunk movement and muscle activity in children with Duchenne muscular dystrophy when performing daily activities

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In performing daily activities from a seated position, besides the upper extremities, the trunk plays a crucial role. For patients with Duchenne muscular dystrophy (DMD) it becomes more difficult over time to perform such activities independently due to muscle weakness. The aim of this study was to gain insight in trunk movement and back muscle activity in patients with DMD in different disease stages, when performing seated daily activities. This knowledge will be used for the development of a dynamic trunk supportive device for these patients. Seventeen participants with DMD (7-20 years) and twenty-five healthy participants (6-20 years) were included in this study. A 3D motion analysis system (Vicon) was used to record 23 single markers on pelvis, trunk and arms. Surface electromyography (EMG) signals were collected of the longissimus, iliocostalis and external oblique muscles and were normalized by maximum voluntary isometric contraction (MVIC) measurements in a seated position. The maximum force was also collected during MVIC. Participants performed several daily tasks, like reaching forward and sideward, drinking and writing. Afterwards, trunk kinematics and muscle activity were calculated. First analyses showed increased trunk movement when reaching within arm length distance for DMD compared to healthy controls. Differences could already be seen in patients with a relatively good arm function (Brooke scale 1). Normalized back muscle activity generally increased with Brooke scale until the task could not be performed anymore. More detailed analyses are ongoing. So, trunk movement is important for boys and men with DMD to perform daily activities. However, with disease progression, this requires an increase percentage of their trunk muscle strength. Clinicians should therefore take the trunk into account and not only focus on the upper extremities.

http://dx.doi.org/10.1016/j.nmd.2018.06.368

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Bringing the spoon to the mouth or the mouth to the spoon? The analysis of compensatory movements of simulated feeding in Duchenne muscular dystrophy: a case-control study

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The difficulty of bringing the spoon to the mouth is frequently reported by people with Duchenne muscular dystrophy. Simulated feeding assessment can reveal several compensatory movements. Such movements are employed to maintain the functional performance when muscular weakness progresses. This study aimed to describe and compare the performance of men with Duchenne muscular dystrophy and age-matched controls (participants aged from 11 to 29 years and volunteers with Duchenne muscular dystrophy were classified as Vignos 1 to 8). Simulated feeding was evaluated by asking volunteers to bringing the spoon to the mouth. The compensatory movements performed during the task were observed and described. Twenty-six people with Duchenne muscular dystrophy and twenty-two healthy controls were filmed while performing the task. Six kinematic variables are used to evaluate the compensatory movements: initial and final angle of head flexion; initial and final angle of elbow flexion; peak velocity and total time. Kinovea software (version 8.25) and Statistica software (version 13.0) were used for movement and data analyses. The kinematic analysis showed that people with Duchenne muscular dystrophy differed from controls in several variables. Analysis of variance evidenced that people with Duchenne muscular dystrophy showed increased initial and final angles of elbow flexion, increased final angle of head flexion and increased total timed performance ($p<0.05$ in all comparisons). In conclusion, the assessment of bringing the spoon to the mouth (simulated feeding) can be used in clinical practice to describe compensatory movements in initial and/or late stages of Duchenne muscular dystrophy.

http://dx.doi.org/10.1016/j.nmd.2018.06.369

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Development of dynamic trunk and head supportive devices for children with neuromuscular disorders

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Performing daily activities independently is becoming more difficult over time for patients with neuromuscular disorders, due to progressive muscle weakness. Seated in a wheelchair, it is important to be able to move the upper body. This is not limited by upper extremity and hand movement, but the trunk and head play also an important role in movement and stabilization. Arm supportive devices are being developed, but the development of and integration with dynamic trunk and head supportive devices is lacking. Therefore the Symbionics 2.1 project aims to develop dynamic supportive devices for trunk and head, that stabilizes the trunk and head while allowing the user to choose postures that support optimal performance of hand/arm activities. Interaction between trunk, head and upper extremity movement was evaluated in 25 healthy children, 18 boys/men with Duchenne muscular dystrophy (DMD) and 17 persons with spinal muscular atrophy (SMA). This

knowledge on movement and muscle activity was integrated in the design of the supportive devices. A passive trunk support device was developed and evaluated with 10 healthy men and 3 boys with DMD. A significant decrease in back muscle activity was seen when flexing the trunk with the use of the device, compared to without using the device. However, the variation was relatively large especially in the boys with DMD. A robotic setup was developed to evaluate different methods to control a robotic trunk supportive device for patients who have not enough muscle force to move. Control with a joystick and a force sensor in the device at chest level showed the fastest movement times, compared to control with force sensor below the feet and electromyography signals from the legs in 10 healthy participants. Measurements with 3 boys with DMD are ongoing. Both a passive and robotic head supportive device are designed and measurements are planned for mid 2018.

http://dx.doi.org/10.1016/j.nmd.2018.06.370

CONGENITAL MUSCULAR DYSTROPHIES

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Review of the natural history of mental development in Fukuyama congenital muscular dystrophy patients, based on a written questionnaire from their families

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Fukuyama congenital muscular dystrophy (FCMD) is characterized by brain malformation caused by abnormal neurocyte migration, and presents with eye manifestations. Ninety percent of FCMD patients have the homozygote insertional mutation of the founder haplotype, and show typical progression of motor functional deficits. However, many patients with a heterozygote mutation show more severe motor and mental functional deficits. Although many prior reports on FCMD patients focused on the natural history of motor development, very few have referenced mental development. We surveyed 49 families of FCMD patients, who belonged to a patient's association, using a descriptive questionnaire. We classified our questions into 4 categories: 1) motor development, 2) social skills, 3) living skills and 4)language development. Forty-nine answers were collected, the median patient age was 7 years (range: 1.3 to 36 years). Twenty-eight patients had the homozygote mutation, 11 the heterozygote, and there was no answer for the other. All motor development milestones were delayed in all patients. Even though 80% of patients achieved single word communication, verbal development reflecting when the necessity for verbal communication arose, yielded a low evaluation in the social skill category. All patients achieved the skills needed for meal consumption more easily than other living skills such as changing their clothes. Many patients never obtained independent gait, while upper limb motions varied among patients. Furthermore, these motor function level affected their mental development. Communication with the others was also found to be an important factor for encouraging mental development. This study is a rare study focusing on the details of the mental development of FCMD. This survey is anticipated to help the families of FCMD patients as they strive to stimulate the development of their children.

http://dx.doi.org/10.1016/j.nmd.2018.06.371

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Clinical characteristics and long-term course of selenoprotein N1 related myopathy in a large multi-centric cohort

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Selenoprotein N1 related myopathies (SEPN1-RM), including congenital muscular dystrophy with rigid spine (RSMD1), multiminicore disease (MmD), desmin-related myopathy with Mallory body-like inclusions and congenital fiber-type disproportion, are autosomal-recessive disorders caused by pathogenic variants in the *SELENON* gene. They are collectively characterized by early onset muscle weakness especially of the axial muscles, respiratory insufficiency often more severe and out of proportion to skeletal weakness, spinal rigidity and scoliosis. Here we present a detailed phenotypic review of 61 patients (2-58 years) with genetically confirmed SEPN1-RM, with long-term follow-up data for 25 of them. Mean age at onset was 2.2 years, with 47/61 patients presenting before age 2 years mostly with hypotonia, poor head/neck control and developmental delay. Over a mean follow up of 4.8 years, a decline from a mean of 33 to 27 on the 40 point Hammersmith ambulant motor scale was noted in 10/19 patients (range 0.7-14.1 years), with an estimated annual change in motor ability scores of -0.55, indicative of a slow motor decline. Ten children of the total cohort (16%) lost ambulation within the first two decades of life. 45/61 patients (74%) developed scoliosis at a mean age of 10.3 years and 18 (29%) patients underwent scoliosis surgery. Weight trends, available for 21 children, showed values below 2nd centile for 10, while nasogastric feeds and/or gastrostomy was needed in 6/61 children (10%). FVC trends, available for 20 children, showed an estimated % change per year of -2.04 (SE 0.46; p value$<$ 0.001). Nocturnal ventilator support was required in 50/61 (82%) at a mean age of 13 years. This study expands our knowledge of the clinical phenotype and long-term course of SEPN1-RM, and highlights the importance of robust and consistent multi-disciplinary assessment and management to improving outcomes in these children.

http://dx.doi.org/10.1016/j.nmd.2018.06.372

P.325

Severe loss of semimembranosus muscle bulk is an early phenomenon in SEPN1-related muscle disorders: toward early recognition of early-onset muscle disorders by imaging

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Marked decrease in semimembranosus muscle bulk has been pointed out as the major hallmark in muscle imaging in SEPN1-related muscle disorders. However, it remained unclear whether this decrease in semimembranosus muscle bulk was present early in muscle development or it was a progressive phenomenon that mainly occurred during childhood. We present two new SEPN1-related muscle disorders and their imaging phenotype. Patient 1: a female patient was evaluated due to repetitive respiratory infections, hypotonia and gross motor delay. She was firstly evaluated in our center at 29 months. Lower limb MRI at 25 months show absence of semimembranosus muscle bulk and mild infiltration in sartorius and soleus. By exome sequencing, compound homozygous missense mutations in *SEPN1* (c.1379C$>$T; p.Ser460Phe) were found. Progressive restrictive respiratory disorder occurred with significant fatigability. At 6 year of age, she suffered a sudden death while sleeping. Patient 2: eleven month-old male patient was studied by progressive generalized hypotonia. Predominant neck extensor weakness was detected. Absence of semimembranosus muscle bulk was found at whole body muscle MRI. In addition, infiltration in gluteus maximum, sartorius, soleus and lumbar erector spine was detected. The imaging findings leads to *SEPN1* sequencing, which demonstrate compound heterozygous mutations (splice-site mutation c.404-1G$>$A and nonsense mutation c.1189C$>$T, p. Gln397*). The early absence or significant loss of semimembranosus muscle bulk is diagnostic hallmark that is useful for early diagnosis of SEPN-related muscle disorders. The specific, early involvement of semimembra-

nosus could indicate a differential expression or role of SEPN1 in this muscle.

http://dx.doi.org/10.1016/j.nmd.2018.06.373

P.326

Minimal clinically important difference for the Motor Function Measure in patients with congenital muscular dystrophy and congenital myopathy

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To determine the minimal clinically important difference (MCID) for the motor function measure (MFM-32) in congenital muscular dystrophy and congenital myopathy patient an observational, retrospective, multicentric study was conducted on 85 congenital muscular dystrophy or congenital myopathy patients, aged 5 to 22 years at the national institute of neurological disorders and stroke of the national institutes of health and 2 French departments of paediatric physical medicine and rehabilitation. Data were collected if at least 2 MFMs were performed (MFM1 and MFM2) within 8 to 36 months of each other and if during MFM2 parents or patients were asked to provide their perceived change in functional status or strength since MFM1. Patients were divided in 3 groups according to their overall assessment of disease evolution: deterioration, stability or improvement. Absolute score changes between MFM1 and MFM2 total score (TS) and each subscore (D1, D2 and D3) were calculated for each patient. The mean score change of each group of patient reported disease evolution was provided and then groups were compared to determine if the difference was statistically significant. The MCID was calculated. Mean scores changes for D1, D2 and TS improved for patients reporting improvement (respectively 2,4±5,6; 2,1±13,3 and 2,5±7,2) and declined for patients reporting deterioration (-3,2±8,1; -1,3±15,7 and -1,3±7,2) or stability (-1,2±7,4; -2,2±10,5 and -1,5±10). The mean score for D3 was stable or improved in all patients, even if they reported an overall deterioration. The MCID was consecutively calculated for D1, D2 and TS. When designing clinical trials in congenital onset neuromuscular diseases, the use of MCID for MFM should be considered as a chief outcome measure to determine if a given intervention effects not only statistically significant change but also clinically meaningful improvements.

http://dx.doi.org/10.1016/j.nmd.2018.06.374

P.327

A model for dominant-mutated collagen VI-related disorder and allele-specific gene silencing therapy

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Primary collagen VI-related disorders (Col6-RD) due to mutations in *COL6A1, COL6A2* and *COL6A3* lead to either a severe Ullrich congenital muscular dystrophy or a milder Bethlem myopathy. Col6-RD is characterized clinically by muscle weakness, respiratory failure, proximal joint contracture, and scoliosis, and pathologically by marked variation in fiber size, scattered muscle necrosis and regeneration, and increased endomysial fibrosis and adipogenesis. Recently, we established mouse models (Δ50 mouse) of an autosomal dominant form of Col6-RD by 50-bp deletion in *Col6a1* gene, which causes the in-frame deletion of whole exon 9 in *Col6a1* transcript. In this study, we further analyzed the phenotypes of the Δ50 mouse models and conducted the allele specific silencing therapy toward the muscle-retained mesenchymal progenitor cells (MPCs). We analyzed muscle pathology of Δ50 mice chronologically on aging. Muscles from Δ50 mice showed enhanced fibrosis from young ages with morphological changes of mesenchymal progenitor cells. Δ50 mice represented the unique spatial localization of collagen VI aggregates near MPCs, which was different from that of perlecan. The efficacy of designed siRNAs for allele-specific gene silencing was measured by *in vitro* luciferase assay on artificial reporter gene constructs. We identified an siRNA which is highly effective and specific to a product from the mutated allele. By treatment with this siRNA, collagen VI localization was recovered around MPCs. Thus, dominant-mutation in *Col6a1* made unique features of collagen VI aggregates in muscles. Allele specific gene silencing by siRNA would be promising therapeutic application for autosomal dominant Col6-RD.

http://dx.doi.org/10.1016/j.nmd.2018.06.375

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Pneumothorax in Ullrich congenital muscular dystrophy

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Pneumothorax (PT) is a rare complication of Ullrich congenital muscular dystrophy (UCMD). To determine the clinical characteristics of UCMD with PT and the histological features of lung tissue in mice with a Col6a1 dominant mutation. Among 25 UCMD patients treated at NCNP hospital, 4 (16%) developed PT. Case 1 was a 16-year-old girl who had received noninvasive positive-pressure ventilation (NPPV) since age 11 years. At age 16 years, she was admitted to the hospital due to chest pain and dyspnea. Chest CT revealed PT, and she was successfully treated with oxygen therapy without recurrence for six months. Case 2 was a 29-year-old man treated with thoracoscopic surgery for tension PT at age 13 years. He had used NPPV since age 16 years and had 8 recurrences of PT. Case 3 was a 29-year-old woman who had received NPPV since from the age of 15 years. At age 23 years, she had 9 episodes of PT, concurrent with menstruation. She died of tension PT at the last recurrence. Case 4 was a 9-year-old girl who had received NPPV since age 7 years. At age 9 years, she was transferred to the hospital because of emesis and decreased consciousness level. She was in shock status on arrival and died despite resuscitative efforts. Postmortem CT revealed PT and free air in the abdomen. Of the 4 patients with UCMD, 3 first developed PT in teens or earlier (median, 14.5 years), 2 had recurrences, and 2 had fatal outcomes. In the lung tissue of mice, localization of collagen VI was different between *Col6a1* mutated and wild-type mice, particularly in the visceral pleura. NPPV use may not always lead to PT. Structure abnormality of the visceral pleura in lung of UCMD patient may lead to pleural fragility and PT. PT can be a complication of UCMD even in the early stage.

http://dx.doi.org/10.1016/j.nmd.2018.06.376

P.329

CALLISTO: a phase I open-label, sequential group, cohort study of pharmacokinetics and safety of omigapil in *LAMA2* and *COL6*-related dystrophy patients

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The anti-apoptotic compound omigapil demonstrated inhibition of GAPDH-Siah1-mediated apoptosis in muscle with concomitant improved weight and locomotor activity in the *LAMA2*-related dystrophy (*LAMA2*-RD) mouse model (dyw/dyw mouse). Studies of omigapil in the *COL6*-related dystrophy (*COL6*-RD) mouse model (*Col6a1*-/- mouse) demonstrated decreased apoptosis, in particular of the diaphragm muscle. A phase I open-label, sequential group, cohort study of omigapil in *COL6*-RD or *LAMA2*-RD patients aged 5-16 years conducted at the NIH with objectives: 1. to establish the pharmacokinetic (PK) profile of omigapil at a range of doses, using a novel adaptive algorithm, SAVOR (stochastic approximation with virtual

observation recursion), to predict the dose associated with a 90% probability of achieving target area under the curve (AUC), 2. to evaluate the safety and tolerability of omigapil at a range of doses and 3. to establish the feasibility of conducting disease-relevant clinical assessments. Twenty patients were randomly assigned to 1 of 3 dosing cohorts, with each patient receiving 4 weeks of vehicle run-in and 12 weeks of study drug (applied at daily doses of 0.02 - 0.08 mg/kg using a liquid formulation) with follow-up 8 weeks after study drug discontinuation. PK data from each cohort was analyzed before each subsequent dosing group was enrolled. The SAVOR design allowed for a practical approach for the dose adjustment between patient groups and supported the escalation/reduction of doses with the possibility to interpolate between pre-specified doses. The trial met its primary objective and established that the PK profile of omigapil is suitable for further development in pediatric patients and demonstrated that omigapil was safe and well tolerated. This is the first clinical trial of a therapeutic compound in *LAMA2*-RD and *COL6*-RD patient populations, completed with an innovative model to support dose adjustments in a dose finding study.

http://dx.doi.org/10.1016/j.nmd.2018.06.377

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Long-term motor function in collagen VI-related myopathies is associated with the maximal motor ability achieved: a classification proposal

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Collagen VI-related myopathies encompass a continuum of overlapping phenotypes ranging from severe Ullrich congenital muscular dystrophy to mild Bethlem myopathy. Categorizing patients with collagen VI-related myopathies into groups from early stages according to expected clinical course is particularly relevant to deepen understand the natural history of the diverse phenotypes and to accurately test the efficacy of therapies, which are currently under development. According to the maximal motor capacity achieved, we stratified the phenotypes of 63 patients with collagen VI-related myopathy into 4 clinical categories. We correlate this classification with the functional status of each of the 4 groups of patients at the current stage. Patients with genetically and/or pathologically confirmed diagnoses of collagen VI-related myopathies were included. Motor function testing included the 6-minute walk test (6MWT), the motor function measure (MFM-32), North star ambulatory assessment (NSAA), and the performance of upper limb (PUL). Motor abilities collected included: 1) Independent walking, 2) rising from floor unassisted, and 3) stair climbing. According to the maximal motor ability achieved, 11/63 patients (17%) were categorized as having Ullrich congenital muscular dystrophy, 14/63 patients (22%) were categorized as moderate progressive collagen VI-related myopathy, 16/63 patients (25%) as intermediate collagen VI-related myopathy, and 22/63 patients (35%) as having Bethlem myopathy. Patients were assessed using functional scales at a mean age of 15.87 (range: 4-60). There was a positive association between the maximal motor ability achieved and all the functional scales (MFM32, NSAA, 6MWT, and PUL) ($p<0.0001$). This study, that correlates maximal motor capacity with long-term motor function, might help to offer a more accuracy prognosis to patients from early years, consequently improving anticipatory care and outcome measure design.

http://dx.doi.org/10.1016/j.nmd.2018.06.378

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Longitudinal changes of motor outcome measures in individuals with *COL6*-RDs and *LAMA2*-RD

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Identification and development of accurate clinical outcome measures for congenital muscular dystrophies (CMDs) are essential for monitoring disease progression and clinical trial readiness. We present results of a longitudinal study of motor outcome measures in children with two types of CMD, *COL6*-related dystrophies (*COL6*-RDs) and *LAMA2*-related dystrophy (*LAMA2*-RD). Over the course of four years 48 individuals (24 *COL6*-RDs and 24 *LAMA2*-RD) ages 4-22 years were evaluated (22 in year 1; 32 in year 2; 38 in year 3 and 4; 36 in year 5). Assessments included the motor function measure 32 (MFM32), myometry (knee flexors and extensors, elbow flexors and extensors) and goniometry (knee and elbow extension). Separate linear mixed effects models were fit for each outcome measurement, with subject-specific random intercepts. Statistically significant results of the two group analyses based on CMD subtypes are presented here: total MFM scores for *COL6*-RDs and *LAMA2*-RD decreased at a rate of 4.36 and 2.93 points respectively each year; all muscle groups for individuals with COL6-RDs decreased between 0.96 and 2.55 percentage points; range of motion measurements of elbow decreased by 3.31 degrees each year in individuals with *LAMA2*-RD, with a loss of right knee extension range by 2.45 degrees each year in individuals with *COL6*-RDs. Further analyses of total MFM by ambulatory status showed significant decreases over time in all groups except for ambulatory individuals with *LAMA2*-RD. Loss of strength as measured by myometry was also evident in all 4 subgroups. Range of motion changes were noted only in the non-ambulant individuals with *COL6*-RDs and *LAMA2*-RD, sparing the ambulatory individuals. Results of this study are an indicator of the applicability of the MFM32 both as an outcome measure for clinical trials for *COL6*-RDs and *LAMA2*-RD, as well as for tracking changes in motor function in these CMD subtypes over time.

http://dx.doi.org/10.1016/j.nmd.2018.06.379

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Dynamic breathing MRI: A promising biomarker of diaphragmatic function in *COL6*-related dystrophy patients and *LAMA2*-related dystrophy patients

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The natural histories of the *COL6*-related dystrophies (*COL6*-RDs) and *LAMA2*-related dystrophy (*LAMA2*-RD) are notable for progressive restrictive lung disease, resulting in respiratory insufficiency with the need for non-invasive ventilation. We sought to explore the application of the imaging modality of real-time cine MRI of breathing, known as dynamic breathing MRI, in children with *COL6*-RDs and *LAMA2*-RD. Dynamic breathing MRI allows for the direct visualization of diaphragm and chest wall movements during breathing. Chest wall and diaphragm magnetic resonance imaging (MRI) was performed on 3T scanners in patients with *COL6*-RDs (n=14), *LAMA2*-RD (n=5) and healthy volunteers (HV) (n=10). Imaging was performed during the basal free breathing state and coached deep breathing. Automated algorithms were used to quantify diaphragm and chest wall movement. Specific CMD subtype diagnosis was significantly related to percent diaphragm excursion ($p<0.001$). Post-hoc analyses showed significant pairwise differences between *COL6* patients and both HV and *LAMA2* patients ($p<0.001$ and 0.001) but not between *LAMA2* patients and HV ($p=1.00$). Diagnosis was also significantly related to percent chest wall excursion ($p<0.01$). Post-hoc analyses of chest wall excursion showed a significant difference between *COL6* and *LAMA2* patients ($p=0.03$) as well as be-

tween *LAMA2* patients and HV ($p<0.01$) but not between *COL6* patients and HV ($p=0.71$). We hypothesize that the chest wall movement area is better preserved in *COL6*-RD patients despite the disproportionate diaphragmatic weakness characteristic of *COL6*-RDs. In contrast, the diaphragmatic movement observed in *LAMA2*-RD patients is better preserved. This may be a mechanism for compensating for decreased chest wall movement as seen in *LAMA2*-RD. These findings suggest that dynamic breathing MRI has the potential to serve as a biomarker of diaphragmatic function in *COL6*-RDs and *LAMA2*-RD as well as a potential outcome measure in future clinical trials.

http://dx.doi.org/10.1016/j.nmd.2018.06.380

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Laminin α1 chain overexpression has potentially broad therapeutic spectrum for *LAMA2*-CMD

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LAMA2-CMD, a devastating form of muscular dystrophy, is caused by mutations in the laminin α2 chain gene. All clinical manifestations associated with the disease elicit suffering and enormous complications in everyday life of patients and their families. Thus, a cure for *LAMA2*-CMD is desperately needed. *LAMA2*-CMD is either a severe, early-onset condition with complete loss of laminin α2 subunit or a milder, late-onset form with partial laminin α2 chain-deficiency. Mouse models dy3K/dy3K (completely devoid of laminin α2 subunit) and dy2J/dy2J (that express a substantial amount of laminin α2 molecule without N-terminal domain) mirror these two variants of *LAMA2*-CMD very well. We have previously demonstrated that laminin α1 chain significantly reduces muscular dystrophy in dy3K/dy3K mice. Among all the different pre-clinical approaches that have been evaluated in mouse models for *LAMA2*-CMD, laminin α1 chain-mediated therapy has been shown to be one of the most effective lines of attack. However, it has remained unclear if laminin α1 chain-driven treatment is also applicable for partial laminin α2 chain-deficiency caused by mutations that lead to truncation of laminin α2 molecule. Hence, we have generated dy2J/dy2J mice overexpressing laminin α1 chain in the neuromuscular system. The laminin α1 chain transgene ameliorated the dystrophic phenotype, restored muscle strength and reduced peripheral neuropathy in 9-week-old mice. Additionally, beneficial impact of laminin α1 chain expression persisted throughout late stages of the disease. Furthermore, dy2J/dy2J mice overexpressing a shorter form of laminin α1 chain also showed significant improvement of the phenotype. These findings provide additional support for the development of laminin α1 chain-based therapy for *LAMA2*-CMD.

http://dx.doi.org/10.1016/j.nmd.2018.06.381

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Recessive loss-of-function mutations in *ITGA7* cause cardiac arrhythmia with or without structural cardiomyopathy and respiratory muscle weakness

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Integrin α7 encoded by *ITGA7* is highly expressed in skeletal and cardiac muscle and contributes to sarcolemmal stability by binding to laminin α2. Three unrelated patients were previously reported with *ITGA7*-linked congenital muscular dystrophy. Here, we report three patients from two unrelated families presenting with adult-onset cardiac arrhythmia and respiratory weakness due to recessive null mutations in *ITGA7*. Patient I, a 51-year-old male presented with delayed motor milestones, stridor since birth, cardiac arrhythmia (frequent ventricular ectopy, non-sustained ventricular tachycardia and premature conduction disease) requiring ICD at 46 years. Cardiac MRI showed basal septal hypertrophy and fibrosis. Examination showed focal wasting of medial gastrocnemii and respiratory impairment. EMG was myopathic. Two other male siblings also reported cardiac symptoms. Patient IIa, a 61-year-old female presented at 49 years with febrile respiratory distress requiring mechanical ventilation and tracheostomy. She had a history of atrial flutter, left bundle branch block and atrioventricular block requiring a pacemaker. She presented with further episodes of relapsing respiratory insufficiency. Examination showed mild weakness of ankle dorsiflexion (MRC 4+) and vocal cord paresis. EMG was myopathic. Muscle ultrasound showed widespread hyperechogenicity in the limb muscles. Patient IIb, her female sibling aged 55 presented with chronic hypoventilation. She had mild limb weakness. Presently she uses nocturnal non-invasive ventilation. Quadriceps biopsies (PI and PIIa) revealed non-specific myopathic changes. Next generation sequencing revealed a homozygous c.806_818del [p.S269fs] variant (PI) and two canonical splice site variants (PIIa, PIIb), (c.2357+1G>A [r.spl?] and c.2278-1G>A [r.spl?]) in *ITGA7*. Immunostaining revealed absent sarcolemmal integrin α7 labeling in both biopsies. Evaluation of α7-integrin-null mice showed a mild progressive myopathy with mainly diaphragmatic involvement and similar pathological features. Patients with predominant respiratory weakness and/or cardiac arrhythmias with or without structural cardiomyopathy should be screened for mutations in *ITGA7*.

http://dx.doi.org/10.1016/j.nmd.2018.06.382

CMT AND NEUROGENIC DISEASE

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Guillain-Barré syndrome subtype diagnosis: a prospective multicentric European study

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There is uncertainty as to whether the Guillain-Barré syndrome (GBS) subtypes, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN), can be diagnosed electrophysiologically. We prospectively included 58 GBS patients. Electrophysiology was performed at means of 5 and 33 days after disease onset. Two traditional and one recent criteria sets were used to classify studies as demyelinating or axonal. Results were correlated with anti-ganglioside antibodies and reversible conduction failure (RCF). No classification shifts were observed, but more patients were classified as axonal with recent criteria. RCF and anti-ganglioside antibodies were present in both subtypes, more frequently in the axonal subtype. Serial electrophysiology has no effect on GBS subtype proportions. The absence of exclusive correlation with RCF and anti-ganglioside antibodies may challenge the concept of demyelinating and axonal GBS subtypes based upon electrophysiological criteria. Frequent RCF indicates that nodal/paranodal alterations may represent the main pathophysiology.

http://dx.doi.org/10.1016/j.nmd.2018.06.383

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Imaging findings in patients with Guillain-Barré syndrome

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To describe magnetic resonance imaging (MRI) findings in patients with Guillain-Barré syndrome (GBS). A retrospective and descriptive study was conducted. The clinical charts of 99 patients with the suspicion of GBS seen between 2013 and 2017 were reviewed. GBS diagnosis was confirmedin 81 patients; 47 without MRIstudies were excluded. Complete MRI with and without gadolinium of the spine was performedin 34 patientsand of the brain in 17. Thickening and enhancement of the anterior and posterior roots of the cauda equina and of the cervicalcordwere assessed on MRI. Median age of the patients was 4 years, ranging from 6 months to 16 years; 23 were boys. MRI was performed between 2 and 37 days after symptom onset (median 6 days). EMG: AIDP 31, AMSAN 1, AMAN 1, normal 1. Thirty of 34 patients (88%) had abnormalities on the MRI. Thickening and enhancement of the cauda equina rootswas seen in 28 (82%) patients: involvement of the anterior and posterior roots in 15 (44%) and anterior roots in 13 (38%); cervical root involvement was observed in 17 (50%). The MRI was normal in four (11%). From those who had posterior root involvement, only 11 experienced pain. Cervical involvement was observed in 17, of whom 15 had upper-limb weakness, however 15 patients with clinical weakness had normal cervical MRI. Cranial nerve involvement was seen in 3 patients, of whom 2 had clinical impairment, but 14 had clinical manifestation without MRI abnormalities. Characteristic features may be observed in MRI, even in the early stages of GBS. Cauda equina root thickening and enhancement are the most common findings. No clear correlation was found either between the imaging findings and disease severity and pain or between cervical involvement and upper-limb manifestations. MRI may be a useful study to support the diagnosis of GBS.

http://dx.doi.org/10.1016/j.nmd.2018.06.384

P.337

Giant axonal neuropathy presenting as CMT2: results from the NIH natural history study

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Giant axonal neuropathy (GAN) is a rare childhood onset neurodegenerative disorder of the peripheral and central nervous system caused by recessive mutations in the *GAN* gene resulting in loss of function of gigaxonin, a cytoskeletal regulatory protein. The true incidence of GAN is unknown but it has been reported in approximately 100 patients worldwide since the identification of the causative gene in 2000. In its classical form GAN displays a consistent phenotype with 'kinky' hair, early gait abnormality from sensory ataxia followed by a progressive length dependent decline in strength with uniform sensory more than motor axonal polyneuropathy on electrophysiology. Patients later develop progressive cerebellar dysfunction, optic neuropathy, respiratory insufficiency and seizures. Death from respiratory complications usually ensues by the 3rd decade. With the advent of whole exome sequencing patients with milder disease, often initially clinically diagnosed with hereditary axonal sensory motor polyneuropathy (CMT2), have been recognized. Here we conduct a careful clinical and genetic characterization of 6 individuals age 8-21 years with genetically confirmed GAN with a milder phenotype who participated in the single site NIH GAN natural history study evaluating 35 patients age 5-21 years. In addition to comparatively better motor function they displayed curly rather than kinky hair, minimal to no brain imaging abnormalities, normal intellect and pulmonary function and no optic neuropathy. No definitive genotype-phenotype correlations emerged. Overall GAN of milder clinical severity can present with a CMT2-like phenotype. Accurate and early diagnosis can be achieved by the inclusion of GAN on CMT NGS panels to facilitate timely initiation of disease modifying therapy, to improve understanding of the natural history of this disorder, and to further elucidate the pathogenic mechanism underlying a milder disease course.

http://dx.doi.org/10.1016/j.nmd.2018.06.385

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X-linked Charcot-Marie-Tooth case with a novel variant in *GJB1*

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X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is caused by the mutation in *GJB1* gene, characterized by the transient central nervous system involvement and long standing peripheral polyneuropathy which does not fulfill the criteria of demyelination or axonopathy. We describe a 37-year-old man with progressive bilateral leg weakness since his early teen. He suffered transient right hemiparesis, followed by quadriparesis at 14 years of age, which was treated with intravenous methylprednisolone and recovered completely in five days. When we examined him at 37 years of age, he presented a distal muscle weakness on lower extremities with sensory symptom. The nerve conduction study demonstrated a motor conduction velocity ranging from 26 to 49 m/s. Brainstem auditory evoked potential revealed a conduction defect between acoustic nerve and lower brain stem. The whole exome sequencing revealed a novel variant c.136 G>A in *GJB1*. This report will raise awareness in this rare disease, which is frequently misdiagnosed early in its course.

http://dx.doi.org/10.1016/j.nmd.2018.06.386

P.339

Preliminary phase 2 results for ACE-083, local muscle therapeutic, in patients with CMT1 and CMTX

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ACE-083 is a locally acting muscle therapeutic based on follistatin that binds myostatin and other muscle regulators. It has been shown to increase muscle mass and force in neuromuscular disease mouse models and to increase muscle mass in healthy volunteers. Charcot-Marie-Tooth (CMT) disease is a hereditary neuropathy characterized by lower leg weakness leading to foot drop and increased risk of falls. This ongoing multicenter, Phase 2 study evaluates the safety, tolerability, pharmacodynamics, efficacy, and pharmacokinetics of ACE-083 in patients (pts) with CMT1 and CMTX with mild-moderate weakness in ankle dorsiflexion. In this two-part study, ACE-083 is administered bilaterally into the tibialis anterior (TA) muscle q 3 weeks. Part 1 is 3-month, open-label with 3 dose-escalating cohorts (6 pts per cohort); Part 2 is 6-month, randomized, double-blind, placebo-controlled (followed by 6-month open-label), and will enroll an additional 40 pts. The primary objective of Part 1 is safety and tolerability; the objectives for Part 2 include muscle volume, strength, function, and quality of life. Data as of 31 Jan 2018 are available for Part 1 Cohort 1 (n=6) treated with 150 mg/muscle and are presented as the average of left and right TA muscles. Median (range) age was 35 yrs (23-62) with 3 male/3 female. Four pts had CMT1A, 1 had CMT1B, and 1 had CMTX. Median (range) duration of symptoms was 31 yrs (14-61) and mean (SEM) baseline fat fraction (FF) was 28.4% (5.8). No serious AEs have been reported and related AEs were primarily injection-

site related and all grades 1-2. Preliminary data show mean (SEM) percent change in total muscle volume from baseline to Day 106 (3 weeks after last dose) of 12.6% (2.9). Mean (SEM) change in FF from baseline to Day 106 was -1.7% (1.2). In summary, local muscle injections of ACE-083 were well tolerated in pts with CMT and resulted in marked increases in muscle volume. Data from all 3 cohorts in Part 1 will be presented at the meeting.

http://dx.doi.org/10.1016/j.nmd.2018.06.387

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Distal arthrogryposis, peripheral neuropathy and an autosomal dominant pedigree leading to a diagnosis of TRPV4-pathy

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Transient receptor potential vanilloid 4 channel (TRPV4) is a calcium permeable cation channel predominantly expressed in bone and peripheral nervous system (PNS). *TRPV4* mutations cause a spectrum of skeletal disorders and PNS syndromes, including Charcot-Marie-Tooth disease type 2C, spinal muscular atrophy, arthrogryposis, and scapuloperoneal spinal muscular atrophy. A 6-year-old boy from a non-consanguineous family was referred to our clinic due to arthrogryposis multiplex congenita (AMC) and weakness of lower limbs. He was not able to walk. There were six other members in the family diagnosed with varying degrees of peripheral neuropathy and short stature including his father and uncle. Physical examination showed muscle weakness in lower limbs with predominantly distal involvement and atrophy. Lower limbs were short. There were flexion contractures of knees and ankles. Deep tendon reflexes were absent in lower limbs. There was neither motor deficit in upper limbs nor cranial nerve involvement. Electromyography showed lower motor neuron involvement. Exome sequencing targeted to genes involved in arthrogryposis revealed a heterozygous mutation in *TRPV4* (c.805C>T; p.Arg269Cys). This mutation is known to be pathogenic in Clinvar database (rs267607146). The mutation was confirmed by Sanger sequencing and cosegregates with the disease in the family indicating that mutation of this gene is responsible for the disease phenotype. TRPV4-pathies represent a heterogeneous group of diseases presenting with skeletal dysplasias and/or peripheral nervous system involvement. Although our patient is grouped clinically as distal SMA with arthrogryposis, there are patients who present with scapuloperoneal SMA and skeletal dysplasia harbouring the same mutation. Despite significant overlaps in presentations, distal arthrogryposis in combination with short stature, skeletal abnormalities, disproportion of upper and lower extremities and neuropathy should be clinical clues for *TRPV4* mutations.

http://dx.doi.org/10.1016/j.nmd.2018.06.388

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Case report: CMT2D with intermediate pattern. an expanding phenotype?

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Pathogenic variants in the GARS gene cause peripheral nerve degeneration and are associated with Charcot-Marie-Tooth (CMT) disease type 2D and distal hereditary motor neuropathies (dHMN) type 5A. These are allelic diseases and familial variants may present either CMT2D or dHMN phenotypes, and are associated with axonal features on electrophysiology studies. We describe a 11-year-old male from Brazil, with complaints of progressive weakness, difficult walking and distal decreased sensation, since he was 8 years old. On examination, distal muscle wasting, decreased deep tendon reflexes and pes planus were also noticed. Nerve conduction studies revealed upper limbs compound muscle action potentials (CMAPs) with reduced amplitudes, moderately increased distal latencies, reduced conduction velocities (averaging from 25.5 to 32.9 m/s) and slightly increased duration on the left ulnar nerve. CMAPs were not obtained on lower limbs. Sensory nerve action potentials were reduced in amplitude and with normal conduction velocity and latencies on all limbs, while electromyography revealed signs of chronic denervation in distal muscles. The findings were classified as an intermediate electrophysiological pattern. Genetic panel for hereditary neuropathies disclosed a novel missense variant (c.794C>A; p.Ser265Tyr) on exon 7 of *GARS* gene. The variant is not present in the population databases (EXAC, GNoMAD, EVS), it is located in a very conserved residue and is predicted to be damaging according MetaSVM and MetaLR. His mother and his maternal half-sister both had distal limb weakness and electrophysiological evidence of distal chronic denervation affecting upper and lower limbs, compatible with dHMN type 5. Although intermediate pattern CMT is commonly associated with mutations of some genes, this is the first report of pathogenic variant on *GARS* leading to such presentation, what indicates an expansion of the phenotype-genotype correlations related to this gene.

http://dx.doi.org/10.1016/j.nmd.2018.06.389

P.342

Molecular characterization in Charcot-Marie-Tooth in Argentina: 121 case series

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Charcot-Marie-Tooth (CMT) is the most frequent illness of peripheral nerve in pediatrics. The greater availability of genetic studies allows the characterization of the genotype and its correlation with the phenotype. To describe the genetic findings in a series of patients with CMT in Argentina. Patients under 18 years old, all with clinical and electromyographic findings compatible with CMT. Depending on the case, a study was completed for *PMP22*, panel CMT90 (*PMP*, *MPZ*, mitofusin, *GJB1*) or expanded panel. It was discriminated according to the symptoms reported before the first year of life, between the year and 10 years and after 10 years, the conduction velocity (NCV) in the motor median nerve was classified as very low (less than 10), intermediate (10-40).) and normal (more than 40). We included 120 cases out of a total of 135, in which molecular diagnosis was made. They were seen between 2006 and 2018. The age was between 5 months and 17 years, a total of 66 men and 58 women. The findings were: 1) Duplication *PMP22*, 94 cases, all starting between 1 and 10 years, 3 with very low NCV, 77 low, 13 intermediate. 2) *GJB1*, 8 cases, beginning 1 to 10 years, normal NCV in 2 and intermediate in 6. 3) *MPZ*, 8 cases, 6 diagnosed in 1st year, NCV very low 3, low 3, axonal 2. 4) *PMP22* deletion, 6 cases all diagnosed in the 1st year, NCV very low in 4 cases and low in 2 cases. 5) Mitofusin 2, 3 cases of beginning in 1st year, 2 axonal cases and 1 low NCV. 6) Senataxine, 1 case of beginning in 1st decade, with normal NCV and axonal commitment. 7) *NEFL1*, 1 case of beginning in 1st year, NCV very low. Genotypic characterization was obtained in 88% of the cases, of which 77% corresponded to CMT1A with *PMP22* duplication. The remaining 21% characterized was included within the CMT90 panel and only 2 patients were characterized through extended panels. The 15 non-genotyped cases could benefit from the use of exome sequencing

http://dx.doi.org/10.1016/j.nmd.2018.06.390

P.343

Colchicine induced neuromyopathy in a patient using concomitant diuretics

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Colchicine is commonly used to treat gout. The common side effects of colchicine include gastroenteritis, blood dyscrasias, and dermatitis; the neuromuscular toxicity associated with colchicines is under-recognized. The char-

acteristic neuromuscular complication is a neuromyopathy, presenting with subacute proximal lower extremity weakness, elevated serum creatine kinase (CK) and electromyography (EMG) showing an "irritable myopathy" and a length-dependent sensorimotor peripheral neuropathy. We present a patient with colchicine-induced neuromyopathy using comcomitant diuretics. An 70-year-old woman with a significant past medical history including hypertension, heart failure with pericardial effusion, liver cirrhosis with ascites, hypothyroidism and hyperuricemia presented to our clinic for evaluation of general weakness for 1 month. The weakness started in the both thighs and lower legs about 4 weeks prior to presentation and progressively worsened. She was on colchicine 1.2 mg per day, which she had been taking for several months for pericardial effusion and hyperuricemia. On examination, cognition and cranial nerves were normal. She had both proximal and distal upper limb weakness, severe hip flexor and dorsiflexor weakness and diffuse lower limb weakness. She had graded sensory loss to pain and cold sensation up to the knees, reduced vibration sensation at the ankles and reduced joint position sensation at the toes. Nerve conduction studies revealed sensorimotor polyneuropathy of axonal type. Needle electrode examination demonstrated fibrillation, postitive sharp and myotonic potentials in distal extremity muscles; motor unit potentials were of varying duration and amplitudes in various muscles diffusely. The neuromuscular complications associated with colchicine are commonly under-recognized. Chronic renal dysfunction or diuretic use makes patients more susceptible to this neuromuscular complication at the usual dose range. Co administration of any drug that is metabolized by the CYP3A4 system can induce colchicine myopathy. The common diagnostic consideration in patients with colchicine myoneuropathy is polymyositis because of predominant proximal weakness, elevation of CK and irritable myopathy on EMG.

http://dx.doi.org/10.1016/j.nmd.2018.06.391

P.344

Lipodystrophy and muscle hypertrophy

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Lipodystrophies are a group of rare disorders characterized by variable loss of body fat and insulin resistance–related metabolic complications. Lipodystrophies can be classified as acquired and hereditary by their etiology. They are also classified as localized, partial or generalized in respect to the fat loss distribution. Neuromuscular involvements such as polyneuropathy, hypertrophic appearance in muscles and myopathy have been reported in lipodystrophies. Herein, we present two siblings with familial partial lipodystrophy. A 29-year-old female admitted to our outpatient clinic with complaint of hypertrophic appearance of muscles in her arms and legs for 9 years. There was no muscle pain or muscle weakness. She was diagnosed with diabetes mellitus one year ago and treated with metformin. On neurologic examination, muscle strength was normal and deep tendon reflexes were decreased in both upper and lower extremities. On laboratory investigation, her creatine kinase level was normal and triglyceride level was high (385 mg/dl). Hepatic steatosis (grade 2) was detected by abdominal ultrasonography. Electromyography revealed demyelinating sensory-motor polyneuropathy. MRI of lower extremity showed subcutaneous adipose tissue atrophy. Her elder sister was 46-year-old. She complained of the hypertrophic appearance of muscles on extremities like as her sister. She was also diagnosed with diabetes mellitus and hyperlipidemia. On her examination, muscle strength was normal and deep tendon reflexes were decreased. Electromyography showed demyelinating sensory-motor polyneuropathy. There was subcutaneous adipose tissue atrophy on extremity MRI. Lipoatrophy and metabolic features are compatible with the diagnosis of familial partial lipodystrophy in these two siblings. Lipodystrophies are a rare group of diseases that cause muscular hypertrophy and other neuromuscular involvements. They should be considered in differential diagnosis in patients with hypertrophic muscles.

http://dx.doi.org/10.1016/j.nmd.2018.06.392

P.345

Serum auto-antibody positivity induced by intravenous immunoglobulin (IvIG) infusion

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Evidence from controlled clinical trials has established IVIG as a first line therapy for inflammatory autoimmune neuropathies such as Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and multifocal motor neuropathy (MMN). Several infusion-related reactions are well documented in the literature, including common reactions such as headache, myalgia and chills. Rare and more serious reactions such as thromboembolic events, acute renal tubular necrosis, and anaphylaxis are also documented. Few data exist on the effects that IVIG has on various autoantibody laboratory values, and the relation these antibodies may have on inducing autoimmune related symptoms. To study the effects of IVIG on various autoantibody laboratory values and whether or not clinical manifestations to these antibodies develop. Three adult patients who received one course IVIG for autoimmune neuromuscular conditions had laboratory evaluation for various autoantibodies immediately before and after completion of the IVIG treatment of 2 gm/kg. These autoantibodies were rechecked 6 weeks post completion of the therapy. In all 3 patients, the autoantibodies were normal at baseline and the titers increased upon completion of the therapy. One patient was symptomatic; the remaining 2 patients were asymptomatic despite elevation of the autoantibodies. The levels returned to normal 6 weeks later. As the result of these findings, we encourage continued investigation of the contents of IVIG and the purification thereof in order to prevent autoimmune related symptoms in some recipients.

http://dx.doi.org/10.1016/j.nmd.2018.06.393

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Small molecule image-based screen identifies modulators of PML nuclear body phenotype in ALS models

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Dominant mutations in the gene encoding the nucleic acid binding protein FUS cause ~5% of familial amyotrophic lateral sclerosis (ALS). While some FUS mutants mislocalize to the cytoplasm due to disruption of a nuclear localization sequence, many remain predominantly nuclear and may exert a gain of toxicity within the nucleus. We seek to discern the mechanism(s) by which FUS mutants ultimately injure aging motor neurons and to develop effective therapeutic approaches to defend against these insults. We identified a novel and robust nuclear phenotype caused by FUS mutants: impaired stress-responsive processing of sub-nuclear assemblies known as promyelocytic leukemia (PML) nuclear bodies. PML nuclear bodies occur in many cell types (including CNS and muscle) and mediate stress-responsive regulation of nuclear protein homeostasis, transcription, DNA-damage pathways, and cellular senescence, yet their potential role in ALS has not been explored. We observed that PML bodies were abnormally enlarged both in cell lines and in human ALS fibroblasts expressing mutant *FUS*. Exposure to mild oxidative stress or proteasome inhibition aggravated this phenotype in FUS mutant cells. We developed a high-content imaging-based assay to screen for small molecule compounds that exacerbate or ameliorate the PML body abnormality. Using the LOPAC library of 1,280 pharmacologically active compounds, we identified a set of hits that implicate impaired cellular redox homeostasis as an important determinant of the phenotype and confirmed this using human ALS fibroblasts. We have established transgenic mice harboring ALS-linked *FUS* variants and observed age-dependent loss of the connection between motor nerves and muscle in mice that express the *hFUS*-R495X mutant. We are using a lentiviral reporter to test whether a subset of the prioritized hit compounds modulate defects of nuclear protein homeostasis in cultured primary neurons, glia, or muscle cells obtained from *FUS* mutant mice.

http://dx.doi.org/10.1016/j.nmd.2018.06.394

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Feasibility and validation of modified oculobulbar facial erspiratory score (mOBFRS) in amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder that results in progressive facial, bulbar, respiratory and limb muscle weakness. The ALSFRS-R is a reliable patient reported outcome measure used in ALS, however, we lack objective scales that can quantitate deterioration in bulbar functions. We are conducting a prospective study to test the feasibility of using, and validate the use of the modified oculobulbar facial respiratory score (mOBFRS) in ALS. We will evaluate if the changes in the mOBFRS in ALS): 1) can be reliably measured on a serial basis; 2) correlate with scores of the existing subjective ALS functional rating scale (ALSFRS-R) and objective bulbar rating scale (BRS); and 3) can be used as a potential outcome measure in clinical trials. Subjects are tested at baseline, month 3 and month 6. Interim analysis was done using Pearson's correlation calculated between mOBFRS, BRS, and ALSFRS-R at each visit. A linear mixed model assessed mOBFRS as the dependent variable and time as the independent variable to capture how the mOBFRS score changed over time. Since study initiation, 120 ALS subjects have been enrolled and 50 subjects have completed the study. The mOBFRS score was negatively correlated with the BRS total score, ALSFRS-R total score, and ALSFRS-R bulbar sub-score at all three visits ($p<0.0001$). Subject's mOBFRS score changed by 2.43 points from baseline to month 6 ($p<0.0001$), showing increased sensitivity compared to the decrease in the BRS score from 0.89 points from baseline to month 6 ($p<0.0621$). The ALSFRS-R swallow ability question was compared to the mOBFRS timed swallow test which showed a medium correlation. Patients tended to underscore their dysphagia when compared to the objective score measured by the mOBFRS. Preliminary results show that the mOBFRS is a sensitive measure and has the potential to be a useful tool in evaluating dysphagia in ALS.

http://dx.doi.org/10.1016/j.nmd.2018.06.395

METABOLIC MYOPATHIES II

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Identification of late-onset Pompe disease with nationwide high-risk screening study in Japan

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Late-onset Pompe disease (LOPD) is a rare, but treatable metabolic myopathy due to acid alpha-glucosidase (GAA) deficiency. LOPD is characterized by progressive muscle weakness and/or respiratory failure, but some LOPD patients without typical signs could be overlooked. To evaluate the utility of Dried Blood Spots (DBS) in the diagnostic work-up and assess the prevalence of LOPD within a Japanese high-risk population, we prospectively screened for LOPD in a Japanese cohort of undetermined myopathy patients aged one year or older with muscle weakness and/or elevated serum creatine kinase levels. Sixteen neuromuscular center hospitals, members of muscular dystrophy clinical trial network (MDCTN), joined the Pompe disease high risk screening study in Japan (PHiRS-J). We tested GAA activity with DBS as first screening method. Patients with reduced GAA activity in DBS were re-analyzed for enzyme activity in lymphocytes, and investigated for GAA gene mutations. Among 164 patients enrolled, two were incompatible with inclusion criteria. Eleven patients showed reduced GAA activity with DBS. Of these patients, three showed normal GAA enzyme activity in lymphocytes; five were revealed as pseudodeficiency; three with confirmed reduction of GAA activity in lymphocytes were identified to have homozygous or compound heterozygous mutations of the *GAA* gene. Two infants with compound heterozygous mutations and a male in mid-seventies with a homozygous mutation were finally diagnosed with LOPD, and they presented only mild muscle weakness without cardiopulmonary failure. In a Japanese high-risk cohort, we found a prevalence of LOPD around 2%. This study suggests that screening of GAA activity with DBS is useful to diagnose patients with LOPD in a high-risk population.

http://dx.doi.org/10.1016/j.nmd.2018.06.396

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Late-onset Pompe disease: still a missing diagnosis?

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Pompe disease (PD) is a lysosomal storage disorder caused by acid alfa-glucosidase deficiency due to mutations in the GAA gene. Late-onset Pompe disease (LOPD) is usually characterised by slowly progressive limb-girdle weakness, respiratory failure and/or hyperCKemia. However, a wide range of phenotypes can be seen. In 2006 alglucosidase alfa was approved as enzyme replacement therapy for PD. Therefore, its prompt diagnosis has become more noteworthy. We aimed to discuss the potential pitfalls in LOPD diagnosis. A retrospective study was performed, including 7 genetic-confirmed LOPD patients followed at our National Reference Centre from January 2007 to December 2017. 3 out of 7 (42.86%) were men and the mean age of onset was 32.29±12.91 years (17-53). A limb-girdle weakness pattern was seen in all. 6 out of 7 (85.71%) had respiratory involvement, being 4 (66.67%) on non-invasive ventilation. Palpebral ptosis and bulbar signs were disclosed only in 2 (28.57%). All except one (85.71%) showed high CK levels. Needle EMG raised doubt about a neurogenic/chronic myopathic pattern in 1 patient with a severe diaphragmatic paresis and absent phrenic motor responses bilaterally, being clearly myopathic in the remaining patients. Muscle biopsy was performed in 4 (57.14%) patients, but the diagnostic suspicion of PD based on histological findings was found in only 1 (25%). Mean time of delayed diagnosis was 20±9.83 years (6-39). Misdiagnosis included limb-girdle muscular dystrophies (3), metabolic myopathy, inclusion body myositis, lumbosacral spinal stenosis and motor neuron disease. According to the literature and our own experience, LOPD remains a challenging diagnosis due to phenotypic heterogeneity, atypical or unspecific findings on muscle biopsy and even pitfalls on needle EMG. Since treatment is available with well-known positive results regarding muscle strength, respiratory function as well as survival, a high index of suspicion for its diagnosis is needed.

http://dx.doi.org/10.1016/j.nmd.2018.06.397

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A novel hybrid promote directing AAV-mediated expression of acid alpha-glucosidase to liver, muscle and CNS yields optimized outcomes in a mouse model of Pompe disease

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Pompe disease is caused by mutations in the acid alpha-glucosidase gene (*GAA*) that is responsible for processing lysosomal glycogen. Patients with Pompe disease exhibit clinical phenotypes across a variety of tissues, including glycogen buildup in cells, deficits in cardiac, respiratory, and skeletal

muscle function, and CNS pathology. We proposed that optimal multi-tissue expression driven by a single gene transfer vector may address the deficits that have been refractory to enzyme replacement therapy and promote immune tolerance to hGAA. To achieve these goals, we designed AT982, a rAAV8 vector containing a novel hybrid promoter to target expression of hGAA to muscle, liver, and nervous system, and tested this vector in a murine *GAA*-/- model of Pompe disease. Mice were dosed with AT982 at 1×10^{13}, 3×10^{13}, or 1×10^{14} vg/kg, and in-life measures and bioanalytical endpoints were assessed relative to vehicle-treated GAA -/- or WT littermate control mice. Assessment of diaphragm, heart, and skeletal muscle tissue indicated dose-dependent increases in hGAA expression and activity, and reduced glycogen accumulation in these tissues. Consistent with an incremental contribution of the liver promoter element in AT982, mice dosed with AT982 exhibited reduced antibody reactivity to hGAA, and increased serum hGAA activity, compared to mice dosed with a control vector containing a muscle-only promoter element. Finally, we observed dose-dependent expression and activity of hGAA in nervous system tissue and evidence for reduction in glycogen levels in the brains of mice dosed with AT982. Our findings represent the first nonclinical application of an engineered hybrid promoter providing tissue-specific neuromuscular transgene expression combined with immune-tolerizing liver expression and support the clinical translation of AT982 as an optimized hGAA vector for AAV gene therapy for Pompe disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.398

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Exploring study design and endpoint selection to evaluate safety, preliminary efficacy, and dose selection of AAV8 gene therapy in patients with infantile and late onset Pompe disease

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Pompe disease is a rare neuromuscular disease in which acid α-glucosidase (GAA) deficiency leads to glycogen accumulation in all tissues. It presents as a spectrum ranging from the severe, rapidly progressive IOPD to the more slowly progressive LOPD. Currently, the only treatment is enzyme replacement therapy (ERT) with recombinant GAA. While ERT improves prognosis, limitations are associated with clinical progression, functional decline, and burden on the lives of patients/caregivers. Gene therapy with AT982 — a recombinant adeno-associated viral vector serotype 8 (rAAV8) expressing human GAA — offers potential for a single administration with targeted GAA expression in the most affected tissues, including skeletal and cardiac muscle and the nervous system. Nonclinical studies demonstrated that IV administration of AT982 to *Gaa* knockout mice produced dose-dependent increases in GAA activity in skeletal and cardiac muscle, liver, spinal cord, and brain; and improved muscle pathology. Here, we describe phase 1/2, open-label, ascending dose studies to assess safety, preliminary efficacy, and dose selection of AT982 in IOPD and LOPD patients. Both trials are designed to assess 3 dose levels to determine the optimal dose in each population. The IOPD trial is planned to only include ERT-experienced patients (n=12), while the LOPD trial will include ERT-experienced (n=12) and -naïve patients (n=5). Both IOPD and LOPD ERT-experienced subjects will receive ERT until confirmation of GAA activity in muscle biopsies and subsequent weaning. Safety assessments include adverse events (AEs), serious AEs, laboratory tests (including immunological parameters), 12-lead ECGs, echocardiograms, vital signs and physical examinations. Primary efficacy endpoints include GAA activity in muscle, serum, lymphocytes, and whole blood; change in GAA protein, mRNA, glycogen content, morphology, and vector copy number. Additional functional, imaging and quality of life endpoints will be discussed.

http://dx.doi.org/10.1016/j.nmd.2018.06.399

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A novel recombinant human acid alpha-glucosidase, ATB200, co-administered with a pharmacological chaperone, leads to greater substrate reduction and improvement in Pompe disease-relevant markers compared to alglucosidase alfa in *Gaa* KO mice

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Pompe disease is an inherited lysosomal storage disorder caused by a deficiency in acid alpha-glucosidase (GAA) activity, and is characterized by progressive accumulation of lysosomal glycogen in cardiac and skeletal muscles. Enzyme replacement therapy using recombinant human GAA (rhGAA), alglucosidase alfa, is currently the only approved treatment for Pompe disease. However, alglucosidase alfa may have limitations in delivery to skeletal muscles due to sub-optimal levels of mannose-6-phosphate (M6P), a carbohydrate that binds cation-independent M6P receptors at the cell surface to mediate enzyme internalization and lysosomal delivery. We have developed a novel rhGAA (designated ATB200) with a significantly higher M6P content compared to alglucosidase alfa; ATB200 is further stabilized by the small molecule pharmacological chaperone, AT2221 (miglustat). In this study, we compared the effects of ATB200, orally co-administered with AT2221 (ATB200/AT2221; co-administration), to those of alglucosidase alfa in *Gaa* knockout (KO) mice. Repeat administration of ATB200/AT2221 resulted in substantially greater enzyme levels in lysosomes and significant glycogen reduction in key skeletal muscles. Importantly, extensive histological analysis of *Gaa* KO mouse muscle showed that ATB200/AT2221 is more effective compared to alglucosidase alfa in correcting overall cellular dysfunction in the endocytic-lysosomal-autophagic pathways, including lysosomal proliferation and autophagic buildup, the two known hallmarks of Pompe disease. Notably, these positive changes correlated well with improvements in muscle strength and muscle fiber size. Collectively, these data indicate that ATB200, stabilized by the pharmacological chaperone AT2221, offers potential advantages over the standard of care, and warrants further investigation as a next-generation treatment in patients with Pompe disease.

http://dx.doi.org/10.1016/j.nmd.2018.06.400

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Dissecting late onset Pompe disease outcomes. What are we measuring?

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Pompe disease is an inheritable lisosomal storage disorder caused by a genetic deficiency in the enzyme acid α-glucosidase. It's characterized by progressive skeletal and respiratory muscle weakness. As in many neuromuscular diseases, several scales and methods are used to measure muscle loss. Loss of muscle strength is not even, some muscle groups are more affected than others. The aim of this study is to compare individual and "inter-subject" outcome variations among LOPD patients. We analyzed 18 patients with LOPD under ERT with different follow up periods. Timed function tests used in each evaluation included timed Gowers, 4 step climb, 10 meter walk and 6MWT. FVC, MIP, MEP were measured, and quantitative muscle testing of knee flexion (KF) and knee extension (KE) were performed. Evaluations were always carried out by the same experienced clinical evaluator (JC). We compared linear regression slopes of the inverse of timing tests relative to the initial measurement. Patients with a mean age of 40.7 +/- 13.1 years by the time of first visit were followed up by 6.2 +/-3.3 years. Linear regression slopes for 10 meter walk time (-0.58%/year), 4 step climb, (-0.31%/year), timed Gowers (-5.1%/year), 6MWT (0.15%/year), KF (1.97%/year) and KE (-2.64%/year). Although variation coefficients are high, KE (148%) and Timed Gowers (173%) were the lowest. The rate of change in time function tests depends on the test. Intra test variability differs widely from test to test. The slope differences also reflect the demands placed on different muscle groups by each task, eg, paraspinal muscles are more needed in standing from supine than in walking. In LOPD timed Gowers is more sensitive, has

less variability and detects changes earlier than the 6 MWT. It is imperative to develop quantitative methods to measure trunk muscle strength.

http://dx.doi.org/10.1016/j.nmd.2018.06.401

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Safety and efficacy of recurrent inspiratory muscle training in late onset Pompe disease

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In autosomal recessive late-onset Pompe disease (LOPD), deficiency of the enzyme acid alpha-glucosidase leads to progressive weakness of limb, axial and respiratory muscles. Despite enzyme replacement therapy, up to about 1/3 of patients demonstrate suboptimal response and have pulmonary decline leading to ventilator dependency. This study evaluates the safety and efficacy of recurrent inspiratory muscle training (IMT) in patients with LOPD. In this monocentric unblinded single-arm study, patients with genetically confirmed LOPD performed a 6-week IMT, using a mobile electronic IMT device. Resistance started at 30% of baseline maximum inspiratory pressure (MIP), and was increased by 10% at every visit every 2nd week. This was followed by a 6-week-non-training-period. For safety, a decline of >15% of FVC was defined as an adverse event (AE). Outcome measures for efficacy targeted pulmonary function tests (PFT), blood gas analysis (BGA), six-minute-walk-test (6MWT) and patientś questionnaires. Patients documented their daily trainings. We enrolled eleven patients. There was no serious AE. Reported AEs included mild myalgia in face and thoracic muscles in 4 patients. 2 patients reported upper airway tract infections. Pre- to post-training, MIP showed highest changes in 72% of patients with an increase of mean 15% and remained stable while detraining period. After training period, in cross-sectional analysis only changes for MIP were significant ($p<0.024$) with moderate effect size (d=0,402). Minimal changes without significance were seen in all other PFTs, BGA, 6MWT and questionnaires. IMT was well tolerated, but myalgia in face and respiratory muscles may have to be expected. A 6-week-training-period may be too short to achieve a meaningful and significant improvement in PFTs or in the patientś perception. Pre- and Post MIP showed significant changes in this short pilot study, so a long-term study should clarify more details of this type of intervention.

http://dx.doi.org/10.1016/j.nmd.2018.06.402

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Glycogen storage disease type IV: a wide clinical range of neuromuscular phenotypes

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Glycogen storage disease type (GSD) IV is an autosomal recessive disorder of carbohydrates caused by a deficiency of amylo-1-4 glycanoglycosyltransferase, leading to the accumulation of poorly branched amylopectin-like polysaccharides in various tissues including the liver, heart and neuromuscular system. The typical presentation is described by failure to thrive, hepatosplenomegaly and lethal liver cirrhosis. The neuromuscular phenotype of GSD IV has a broad range of severity. Three different types are known: 1) antenatal onset, fetal akinesia deformation sequence (FADS) or arthrogryposis multiplex congenita (AMC) and perinatal death, 2) severe congenital myopathy and 3) delay of motor milestones and proximal muscular weakness. Additionally, there are intermediate forms, which seem to have been underestimated so far. To describe the phenotype in our 3 patients (1 boy/2 girls; age: 18 months-10 years) with genetically confirmed GSD IV due to heterozygous mutations in GBE1 gene and demonstrate the diagnostic work-up including results of muscle biopsies. Two patients showed a phenotype with antenatal onset, AMC, reduced muscle bulks, swallowing difficulties and severe muscular weakness with a very slow motor development. One patient had an unusual course with AMC, early improvement with mild motor developmental delay (walking at the age of 3 years) and scoliosis. In this patient, two muscle biopsies showed no specific pattern in light microscopy. Ultrastructural analysis of the second biopsy disclosed small, cytoplasmic bodies. None of the patients developed cardiomyopathy, hepatopathy or respiratory distress. Currently, the clinical range of GSD IV seems to be wider than known. Therefore, the diagnostic work-up should necessarily include a detailed description of the phenotype. AMC should be the important diagnostic clue to guide the genetic analysis of the GBE1 gene.

http://dx.doi.org/10.1016/j.nmd.2018.06.403

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Lower limb muscle strength and function in a cross-sectional study of patients with glycogen storage disease type IIIa

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Glycogen storage disease type IIIa (GSDIIIa) is an autosomal recessive disorder caused by mutations in the *AGL* gene coding for the glycogen debranching enzyme. The symptoms start in childhood with liver involvement and progress at adulthood with skeletal muscle weakness that can lead to ambulation loss. This cross-sectional study focusses on lower limb muscle strength and function evolution with age. Torques were measured at the knee and ankle joints by the Biodex and the MyoAnkle dynamometers, respectively. Muscle function was assessed by the motor function Mmeasure (MFM) scale and by the 6-minute walk distance (6MWD). Relationships between age, torques and functions were assessed by Spearman correlation coefficients (rS). The data of 33 patients (52% males) aged of 29 ± 17 (range 11-68) years old were analysed. Age was correlated with torques of knee extension ($rS=-0.38$, $p < 0.05$, $n=33$), ankle dorsi- ($rS=-0.73$, $p < 0.001$, $n=31$) and plantarflexion ($rS=-0.56$, $p < 0.01$, $n=31$) expressed in percentage of predicted value (%pred). Age was also correlated with function assessed i) by the MFM scores for D1, D2, total and items 4 (ankle dorsiflexion), 28 (heel walk), 30 (run), 31 (hop on one leg) ($-0.64 \leq rS \leq -0.45$, $p < 0.01$, $n=33$) and ii) by the 6MWD in absolute value ($rS=-0.54$, $p=0.001$, $n=33$) but not in %pred. The 6MWD (%pred) was correlated with all the muscle torques (%pred) and function parameters ($0.50 \leq rS \leq 0.81$, $0.0001 < p < 0.01$, $31 \leq n \leq 33$). Ankle dorsi- and plantarflexion torques (%pred) were strongly correlated ($rS=0.81$, $p < 0.001$, $n=31$) and also correlated with knee extension and flexion (%pred) ($0.48 \leq rS \leq 0.70$, $p < 0.01$, $n=31$). MFM items 4, 28, 30 and 31 were correlated with ankle dorsi- and plantarflexion ($0.49 \leq rS \leq 0.68$, $p < 0.01$, $n=31$). A progressive weakness in ankle dorsi- and plantarflexors and in knee extensors develops with age, accounting for the progressive loss of function in lower limbs.

http://dx.doi.org/10.1016/j.nmd.2018.06.404

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Expression analysis of glycogenin-1 and glycogenin-2 in patients with glycogen storage disease XV

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Glycogen storage disease type XV (GSD15) is caused by mutations in the *GYG1* gene, which encodes glycogenin-1, a primer for biosynthesis of glycogen. Patients with *GYG1*-mutations are characterized by either absent or non-functional glycogenin-1, and storage of glycogen or polyglucosan in skeletal muscle. There is also storage in the heart in some patients with cardiomyopathy. Despite the fact that glycogenin-1 is considered to be required for glycogen synthesis, glycogen is present in muscles of glycogenin-1 deficient patients. A role of glycogenin-2 as an alternative primer for glycogen synthesis has been suggested. While glycogenin-1 is ubiquitously expressed, glycogenin-2 is mainly expressed in the liver. To investigate the importance of

glycogenin-1 and the role of glycogenin-2, we performed western blot analyses, mass spectrometry, and immunohistochemistry on tissue specimens from *GYG1*-mutated patients and controls. Expression of both glycogenin-1 and glycogenin-2 was present in control liver specimens, but only glycogenin-1 was identified in heart and skeletal muscle of controls. In patients with truncating *GYG1*-mutations neither glycogenin-1 nor glycogenin-2 was expressed in skeletal muscle. However, glycogenin-1 but not glycogenin-2 was identified in the heart of patients with cardiomyopathy due to *GYG1* missense mutations. Immunohistochemistry demonstrated that glycogenin-1 was localised to the storage of glycogen or polyglucosan in cardiomyocytes. In conclusion, glycogen can be synthesised in the absence of glycogenin-1 and up-regulation of glycogenin-2 does not compensate for glycogenin-1 deficiency. Absence of glycogenin-1 leads to accumulation of glycogen and polyglucosan in skeletal muscle fibers. Expression of glycogenin-1 with missense mutations is deleterious to the heart and leads to storage of glycogenin-1 and abnormal glycogen.

http://dx.doi.org/10.1016/j.nmd.2018.06.405

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The diagnostic value of hyperCKemia induced by the non-ischemic forearm exercise test

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The non-ischemic forearm exercise test was developed for a safe and specific screening of patients with exercise intolerance. Some patients with normal tests presented a hyperCKemia 24 hours after the test. The aim of this study was to explore whether this increase was a hallmark of a disease and could be potentially useful for diagnosis. We retrospectively analysed all the patients who performed the non-ischemic forearm exercise test at the Institute of Myology between 1999 and 2016 and who presented a significant increase in CK 24 hours after the test. CK levels were considered significantly increased if their level rose by more than 300 UI/L 24 hours following the test. On 1486 subjects who performed a non-ischemic forearm exercise test, 56 (3.8%) had an increase of CK level 24 hours after. Among these 56 patients, 15 had no raise in lactate level related to glycogenosis V. For patients with normal elevation of lactates, 19 had a muscular dystrophy secondary to mutations in *ANO5, DMD, FKRP, PLEC, SGCA, CAPN3* or *DYSF* genes. HyperCKemia is rare after a non-ischemic forearm exercise test. A normal elevation of lactates associated with hyperCKemia may indicate a muscular dystrophy with a pseudo-metabolic presentation.

http://dx.doi.org/10.1016/j.nmd.2018.06.406

FSHD / OPMD / EDMD / DMI

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Evaluation of dynamic movement orthoses (DMO) as a means to relieve pain and fatigue in patients with facio-scapulo-humeral muscular dystrophy

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Chronic pain and fatigue in the shoulder girdle and upper and lower back are significant and disabling symptoms in patients with FSHD.Short boleros and prefabricated orthoses are used to improve function and reduce pain but they are used randomly with no systematic reporting of effect. The aim of the study was to assess whether a customized, long DMO vest can reduce pain and fatigue in patients with FSHD and to gather information on its usefulness, tolerance and comfort when used in daily activities. Ambulant patients with FSHD aged 20-40 with regular pain in shoulder girdle and/or back and living in the Aarhus area (n= 11) were invited to participate in the study; patients should be able to raise a glass of water to mouth (Brooke-UL score $\leq$ 3) and be motivated for an orthosis. Patients were assessed by Brooke UL and manual muscle test (MRC) of shoulder muscles; they filled in questionnaires on pain (Brief Pain Inventory), fatigue (Checklist of individual strength) and upper limb activities (DASH) before and after the eight-week study period. An orthotic engineer customized a DMO vest to each patient who in the study period registered pain, fatigue, and usefulness of the DMO. After ten weeks, patients were interviewed about effect and usefulness. All 11 persons accepted the invitation (mean age 31.7 y); eight patients completed the study period. Median Brooke score was 3, MRC% in shoulder muscles was 61, the dominant arm tending to be weaker than the non-dominant. Pain and fatigue scores were high with pain interference tending to a decrease after implementation of DMO. Patients reported fewer difficulties with daily life activities (DASH) after the study period although they all said the orthosis felt uncomfortable in the armpits and that it was not suitable for all daily activities. A DMO orthosis may relieve pain and fatigue in patients with FSHD but must be customized individually. It is not suitable and effective for all daily activities.

http://dx.doi.org/10.1016/j.nmd.2018.06.407

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Longitudinal MR evaluation of inflammatory lesions in muscle of patients with facioscapulohumeral muscular dystrophy

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Facioscapulohumeral dystrophy (FSHD) is a muscular dystrophy characterized by progressive weakness and atrophy of facial, scapular and proximal arm muscles. Muscle affection is often asymmetric and progression is often stepwise and not continuous as in most other muscular dystrophies. It has been suggested that muscle inflammation contributes to the pathophysiology of FSHD and that it predates the destruction of muscle and its conversion to fat tissue. However, the duration of inflammatory lesions in muscle and whether they always progress to destruction of muscle in FSHD is unknown. Using Dixon and STIR MRI, we aimed to shed light on the pathophysiology of FSHD by following inflammatory lesions with sequential MRI over 2 years in patients with FSHD. The questions we asked are: can healthy muscle progress to fat degeneration without inflammation; can inflammation be resolved without degeneration of muscle; are inflammatory lesions invariably followed by fat degeneration of the muscle? Patients with FSHD were followed over 2 years with 9 sequential evaluations. The Dixon MRI technique was used to quantify fat content of leg muscles. STIR sequences and T2 mapping were used to detect inflammation. Muscle strength was assessed with a stationary dynamometer. Ten FSHD patients (28-62 years) were included. The study is ongoing. Eight patients have completed all evaluations, one patient discontinued after 6 evaluations and the last patient is still active in the study and has been examined eight times. Data from STIR sequences after visit 8 show a total of 70 $STIR^+$ lesions indicating inflammation: 66 of these were present at visit 1 and 56 at visit 8. Preliminary data indicate that muscles with $STIR^+$ lesions had a higher increase in fat content over time than muscles without lesions. The highest increase in fat content was seen in the few $STIR^+$ lesions that disappeared. Final data, including results from T2 mapping, will be presented at the congress.

http://dx.doi.org/10.1016/j.nmd.2018.06.408

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Estimating thigh muscle volume using bioelectrical impedance analysis with reference to contractile muscle volume assessed by nuclear magnetic resonance imaging

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Availability of noninvasive and highly accurate methods for assessing skeletal muscle mass (SMM) in human is critical in general population and conditions implicating primary and/or secondary muscle wasting. Conventional methods using bioelectrical impedance analysis (BIA) for estimating appendicular SMM oversimplify limb geometry and bioelectrical properties of tissues, relying on sample-specific statistical models rather than biophysical principles. Alternate mathematical models relying on multiple BIA measurements have been proposed and were demonstrated to outperform conventional approaches. However, the influence of intramuscular fat on muscle volume estimates derived from these methods remain unclear. In this pilot work, eight healthy subjects (4 men, 4 women; 37 ± 8 years) and one patient with facioscapulohumeral dystrophy (37 years) underwent quantitative nuclear magnetic resonance imaging (NMRI). Fat fraction maps were acquired in the thighs. After muscle segmentation, overall (NMRI-V) and contractile (NMRI-CV) muscle cross-sectional volume were computed. Subsequently, BIA-based muscle volume (BIA-V) was estimated from seven BIA measurements along the thigh. NMRI-V, NMRI-CV and BIAV were 2215 ± 577, 1944 ± 703, and 1915 ± 712 cm3, respectively. No systematic bias was detected between NMRI-CV and BIA-V (P = 0.49). For NMRI-V vs. BIA-V, intra-class correlation coefficient (ICC) were 0.90 (95% CI [0.71, 0.97]) and standard error of measurement (SEM) was 223 cm3 (95% CI [160, 368] cm3). When comparing NMRI-CV and BIA-V, ICC was 0.99 (95% CI [0.96, 1.0]) and SEM was 85 cm3 (95% CI [61, 140] cm3). These findings confirm the potential of multiple BIA measurements modeling for estimating appendicular SMM. These results also stress the importance of correcting for intramuscular fat in forthcoming validation studies.

http://dx.doi.org/10.1016/j.nmd.2018.06.409

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Regulation of facioscapulohumeral muscular dystrophy candidate protein DUX4

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The *DUX4* gene associated with Facioscapulohumeral muscular dystrophy (FSHD) encodes a toxic transcription factor. Mechanisms that may confer toxic properties to the DUX4 protein are unknown. Characterizing biochemical properties of the DUX4 protein, including addressing whether DUX4 is post-translationally modified, will provide fundamental information required to design FSHD therapies aimed at inhibiting DUX4 protein. We have characterized the following biochemical properties; (1) DUX4 post-translational modifications: We performed mass spectrometry to identify DUX4 post-translational modifications (PTMs) followed by mutagenesis to determine the impact of these modified residues on DUX4 protein stability, toxicity, function, subcellular localization and biomarker expression. We have found a single methylated residue and phosphorylated residues within or near the double homeodomains alter DUX4′s function and toxicity without altering DUX4 protein stability or nuclear localization; (2) DUX4 modifying enzymes: To identify proteins that may interact with DUX4 transiently or indirectly (e.g. transcriptional complex) we performed Rapid Immunoprecipitation Mass Spectrometry of Endogenous Proteins. Additionally, we have quantified the activity of 245 human kinases on DUX4 *in vitro*. Our screen identified 92 kinases that significantly phosphorylate DUX4 protein and 13 exhibit very high activity. We are overexpressing these kinases in myoblasts and determining their impact on DUX4 toxicity. Additionally, we identified a class of modifying enzyme inhibitors that reduce DUX4 toxicity in human myoblasts and are continuing to screen commercially available inhibitors targeting DUX4 modifying enzymes. Our goal has been to investigate modifying enzyme contribution to DUX4 toxicity in FSHD muscle. Importantly, we report for the first time a pattern of PTMs that regulate DUX4 protein function, as well as a modifying enzyme class that when inhibited prevents DUX4-induced toxicity.

http://dx.doi.org/10.1016/j.nmd.2018.06.410

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Progressive myopathy in a new mouse model of facioscapulohumeral muscular dystrophy facilitates development of targeted molecular therapies

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Autosomal dominant Facioscapulohumeral muscular dystrophy (FSHD) is among the most prevalent muscular dystrophies, estimated to affect 1 in 8,333-20,000 individuals worldwide. FSHD is linked to aberrant expression of the *DUX4* gene, which encodes a myotoxic transcription factor. Since DUX4 is extremely toxic, animal model development has been difficult, but progress has been made, revealing that tight regulation of DUX4 expression is critical for creating a viable model that develops myopathic features that are useful as therapeutic outcome measures. Here we report an inducible FSHD mouse model – called TIC-*DUX4* - that utilizes Tamoxifen (TAM)-Inducible CRE recombinase to turn on *DUX4* in skeletal muscle. Uninduced TIC-*DUX4* (i.e. *DUX4*-off) mice are born in Mendelian ratios, develop normally to adulthood, and are indistinguishable from wild-type animals. Induced animals display significantly reduced skeletal muscle force, impaired open field activity, muscle wasting, and histological indicators of muscular dystrophy, including increased central nuclei and inflammation. Importantly, these phenotypes are tunable; myopathy progresses slowly over many months at low doses of TAM, while high doses can be used to rapidly induce widespread myopathic phenotypes within 2 weeks. Vehicle-treated TIC-*DUX4* controls show no functional deficits. We are now using this model to test DUX4-targeted gene therapies and myostatin inhibition to prevent DUX4 induced muscle weakness and increase muscle strength respectively. To directly target DUX4 expression, we utilized the RNAi pathway by AAV delivery of a DUX4-targeted microRNA. This provided long-term protection from DUX4-associated damage in old TIC-*DUX4* mice. We also tested AAV delivery of follistatin, which increased muscle mass and function in induced TIC-*DUX4* mice. These data will support translation of gene therapies for FSHD, and the TIC-*DUX4* mouse model will be useful for testing other FSHD therapies as they emerge.

http://dx.doi.org/10.1016/j.nmd.2018.06.411

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Natural microRNAs as potential modifiers of DUX4 toxicity in facioscapulohumeral muscular dystrophy

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Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant muscle disease associated with progressive weakness in muscles of the face, shoulder-girdle and arms. FSHD arises from an epigenetic defect that ultimately causes aberrant expression of the transcription factor DUX4 in skeletal muscles. DUX4 is toxic to muscle and numerous non-muscle cell types, and causes differentiation defects, muscle atrophy, oxidative stress and cell death. However, FSHD symptoms are often variable from person to person, and there may be also variability in severity of symptoms, rate of progression and age at onset, even in families with several affected relatives. Asymmetry is often seen, where a person may have more muscle weakness on one side of the body versus the other. Although DUX4 is toxic, some cells and tissues seem to resist its damaging effects. We hypothesize that FSHD variability and the differential toxicity of DUX4 are linked; it is possible that the toxic effects of DUX4 may be reduced in cells or muscles that are spared in FSHD. However, the mechanisms by which some cells might resist DUX4 damage are unclear. In this work, we investigate the hypothesis that natural microRNAs could reduce DUX4 expression, reduce its toxicity, and potentially slow FSHD progression. H19 is a long non-coding RNA (lncRNA) that has been shown to promote muscle differentiation and regeneration through the function of its two encoded miRNAs (miR-675-5p and -3p). In this work, we investigated the potential role of H19 and its miRNAs

to counteract DUX4 pathogenicity. We show that miR-675-5p is capable of reducing DUX4 gene expression and associated cytotoxicity *in vitro*. We also show that miR-675-5p acts directly on DUX4 by binding to its transcript and reducing its protein expression. Accordingly, we anticipate that by overexpressing H19 or its miRNAs *in vivo*, in our newly characterized inducible DUX4 mouse model, we would observe reduced muscle toxicity by directly targeting DUX4, and enhanced muscle strength by inducing regeneration and differentiation. This could raise the potential of using these miRNAs to treat FSHD, and would trigger us to investigate their role as genetic modifiers. This proof-of-principle also supports the identification of the full set of natural DUX4-targeted miRNAs that would represent a set of potential miRNA therapeutics or drug targets.

http://dx.doi.org/10.1016/j.nmd.2018.06.412

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Results for a dose-escalation phase 2 study to evaluate ACE-083, a local muscle therapeutic, in patients with facioscapulohumeral muscular dystrophy

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ACE-083 is a locally acting muscle therapeutic based on follistatin that binds myostatin and other muscle regulators. ACE-083 increased muscle mass and force in mouse models and muscle mass in healthy volunteers. Facioscapulohumeral dystrophy (FSHD) is characterized by weakness in various muscles, including those of the upper arm and lower leg. We are conducting a 2-part trial of ACE-083 in patients with FSHD; Part 1 is open-label, ascending dose and Part 2 is double-blind, placebo-controlled. Here we report results from Part 1. ACE-083 (3 cohorts, 150-240 mg) is injected into either the tibialis anterior (TA) or biceps brachii (BB) muscle q3weeks X5 doses, unilaterally or bilaterally. The primary objective of Part 1 is safety, and objectives for Part 2 include muscle volume, strength, function, and quality of life. Data were available as of 15Mar2018 for Cohorts 1 and 2. For the TA Cohorts 1 and 2 (n=12), median age (range) was 46 yr (19-63), median (range) duration of symptoms was 26 yr (4-35), and mean (SEM) baseline fat fraction (FF) was 40.5% (7.5). Adverse events (AEs) included transient injection site reactions and myalgia, primarily grade 1-2; there were no serious AEs. One patient experienced a related grade 3 non-serious adverse event of lower leg intramuscular swelling. At Day 106, 3 weeks after last dose, the mean (SEM) percent change in total muscle volume (TMV) was 8.1 (3.5) for the 150mg cohort (n=6), 16.8 (3.0) for the 200mg cohort (n=6), and 12.4 (2.6) overall (n=12). Mean (SEM) absolute change in FF was -4.5% (3.0) for the 150mg cohort (n=5), -5.0% (2.8) for the 200mg cohort (n=6), and -4.8 % (1.9) overall (n=11). Data for BB are under analysis and will be presented at meeting. ACE-083 treatment was generally safe and well tolerated in patients with FSHD and resulted in increased muscle volume and decreased fat fraction. These preliminary findings support continued investigation of ACE-083 in neuromuscular disorders. Data from all 3 cohorts in Part 1 will be presented at the meeting.

http://dx.doi.org/10.1016/j.nmd.2018.06.413

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BB-301: a single "silence and replace" AAV-based vector for the treatment of oculopharyngeal muscular dystrophy

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OPMD is an autosomal dominant disorder that impacts the muscles of the eyelids and pharynx, leading to ptosis and dysphagia respectively, as well as can lead to proximal limb weakness. The disease is caused by an abnormal expansion of alanine-encoding trinucleotide repeats in the coding region of the *PABPN1* gene. Previously, we described a gene therapy approach to treat OPMD using two AAV vectors. These vectors were tested in the A17 mouse which expresses a bovine *PABPN1* with an expanded polyalanine tract and recapitulates most of the features of human OPMD patients including a progressive atrophy and muscle weakness associated with nuclear aggregates of insoluble mutant *PABPN1*. Here we now describe the development of BB-301, a single vector "silence and replace" therapeutic comprised of an AAV9 capsid to deliver a recombinant genome that uses a muscle specific promoter to produce a bifunctional RNA that expresses shRNA against PABPN1 as well as a codon-optimized shRNA-insensitive wildtype PABPN1. In a 20-week experiment, treatment of TA muscles with BB-301 at 6e10 vg/muscle results in robust inhibition of mutant PABPN1 expression by up to 87% and restores wildtype PABPN1 levels up to 91% of endogenous levels. Concomitantly, BB-301 treatment resulted in correction to near wildtype levels of intranuclear inclusions, fibrosis, and muscle strength as assessed by maximal force. A follow-on 14-week dose ranging experiment was performed at a dose range from 4e8 vg/muscle to 7.5e11 vg/muscle. Mid-ranged doses of BB-301 resulting in 75% inhibition of mutant PABPN1 and 26% restoration of wildtype PABPN1 produce full phenotypic correction of muscle strength and muscle weight, suggesting a broad therapeutic window. Ongoing safety studies are being performed by direct injection into throat muscles in sheep in order to support a first-in-man study, in which BB-301 will be injected directly into the cricopharyngeus muscle for treatment of OPMD-related dysphagia.

http://dx.doi.org/10.1016/j.nmd.2018.06.414

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Clinical characteristics of 4 patients with childhood-onset reducing body myopathy in Japan

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FHL1 mutations are associated with reducing body myopathy; however, the number of case reports with childhood onset is limited. To investigate the clinical characteristics of patients who had reducing bodies in muscle biopsy and *FHL1* gene mutations. Of the 939 patients who underwent biopsy at the age of 15 years or younger since 2000, 4 who had reducing body myopathy were selected. Age at onset, sex, clinical symptoms, CK level, muscle imaging findings, histological findings, and gene mutations were examined. Two cases had early childhood onset, and the remaining had late childhood onset. The cases of early childhood onset were diagnosed as myositis due to rapid progression of muscle weakness. CK level was 287-1050IU/L. Muscle biopsy showed mild to marked necrotic and regenerating fibers with reducing bodies. Case 1; 1-year 4-month-old boy developed cervical instability and progressive proximal muscle weakness. He had difficulty in standing at the age of 1 year 7 months. Muscle MRI revealed diffuse STIR high intensity in lower extremity. Case 2; 1-year 6-month-old girl developed a gait disturbance. She had difficulty in standing at 2 years. She developed respiratory failure and required NPPV and died from asphyxia at 3 years. Case 3; 10-year-old boy developed a gait disturbance. He was diagnosed as limb-girdle muscular dys-

trophy. Muscle CT revealed fatty replacement in the neck, trunk, and thigh. He became wheelchair user at 13 years and required NPPV from 19 years. Case 4; 13-year-old boy became slow in running. He had rigidity in the neck and trunk. He was diagnosed as ankylosing spondylitis. Muscle CT revealed findings similar to those in case 3. He became wheelchair user at 19 years and required NPPV from 30 years. We should consider the MAG staining in the muscle biopsy for the accurate diagnosis and treatment of reducing body myopathy.

http://dx.doi.org/10.1016/j.nmd.2018.06.415

P.369

A Chinese case of the early onset recessive Emery-Dreifuss-like phenotype without cardiomyopathy

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Recently, a new phenotype named the early onset recessive Emery-Dreifuss-like phenotype without cardiomyopathy was reported. The pathological gene responsible for the phenotype was located in TTN gene. Herein, we would like to report a Chinese patient with similar clinical manifestations. A 12 years old boy complained about mild difficulties in climbing and standing up from the ground since the age of 6, and muscle weakness progressed slowly with time. When he came to our clinic, he had lost the ability of walking on the heel. There was no obvious motor dysfunction in upper limbs, except for IV muscle strength of triceps brachii. Thus, weakness of bilateral distal lower limbs was prominent. Furthermore, it was hard to flex neck and extend ankle because of contractures. The malformations of feet were observed, such as pes cavus and overlength of index toes. The level of creatine kinase was 378 U/L. Muscle MRI indicated fatty infiltration and edema in the muscles of bilateral thighs and calves, but the interior group of thigh muscles was spared. The molecular analysis indicated compound heterozygous mutations in *TTN* gene: c.30206dupC (p.E10070Rfs*24) inherited from mother and c.21274T>C (p.C7092R) inherited from father. Additionally, mutations in genes related with Emery-Dreifuss muscular dystrophy (*EMD, LMNA, SYNE1, SYNE2, FHL1*) were not found. This patient has similar manifestations compared with previous reported cases but also some exclusive characteristics, which contributes to the phenotype spectrum of *TTN* gene mutation.

http://dx.doi.org/10.1016/j.nmd.2018.06.416

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Diffusion tensor imaging and voxel based morphometry correlates with the CTG repeats and motor function in adult onset myotonic dystrophy type 1

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Myotonic dystrophy type 1 (OMIM: #160900) is a multisystem disorder that affects the muscle, eye, heart, endocrine system and central nervous system. DM1 is known to show cognitive decline and conventional brain magnetic resonance imaging (MRI) studies also show abnormality in the white matter of DM1 in accordance to cognitive decline. The purpose of our study was to investigate the white and grey matter abnormalities in relation to the clinical aspects with emphasis on the motor performance and corticospinal tract in DM1 Eighteen patients (8 male, 10 female) with DM1 and twenty healthy controls (9 male, 11 female) participated for this study. The clinical characteristics, CTG repeat expansions, handgrip, age of onset, disease duration, laboratory findings including creatine kinase were also obtained. The motor function of the patients was evaluated by Medical Research Council sum score (MRCSS). Imaging acquisition was performed in a 3 Tesla MRI that measured voxel based morphometry, diffusion tensor imaging (DTI) and segmental tract analysis. The mean age of onset was 27.89 years and the mean CTG length was 360. The mean of disease duration was 16.33 years. The CTG repeat significantly correlated with middle occipital and lunatus sulcus bilaterally, right lateral orbital sulcus, and right posterior ramus of the lateral sulcus. These gray matter regions showed a significant volume decrease in DM1 patients. The CTG repeats also showed significant correlation with the posterior limb of the internal capsule (IC). Interestingly, the FA of the posterior limb of the IC correlated with both MRCSS and 6 MWT that reflect the motor performance in DM1. Furthermore, hand grip correlated with various cortical gray matter regions including precentral and postcentral prefrontal cortex with statistical significance. The novelty of our study is that this is the first study that illustrates the relationship between motor performance in DM1 and microstructural abnormalities through volumetry analysis, DTI and segmental tract analysis. In conclusion, 6MWT MRCSS and hand grip well correlated with the corticospinal tract in DM1 with most preferential involvement in the pre and post central area of the prefrontal cortex, reflecting early microstructural involvement of the motor tract.

http://dx.doi.org/10.1016/j.nmd.2018.06.417

P.371

Do scientific publications fit with DM1 individuals expectations? - A systematic review and comparative study

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In the past years, the scientific knowledge on DM1 phenotype and disease progression has greatly improved. In parallel, patients reported data and rare diseases foundation-driven initiatives have contributed to better address patient needs and expectations. To explore the relevance of current DM1 scientific research areas, we designed a study aiming to compare the research areas of interest reported in literature with (i) disease symptoms prevalence and (ii) patients' expectations. We first conducted a systematic review of the literature to categorize the DM1 disease domains studied by researchers. Then, the results were compared with (1) the prevalence of DM1 symptoms in a large cohort of adult patients (n=2469) from the DM-Scope national registry, (2) Quality of life assessment using the InQoL questionnaire in DM1 individuals (n=190), and finally (3) self-reported data collected in the AFM-Telethon foundation DM1 nationwide survey (n=1100). We show that scientific publications topics do not fully cover the range of symptoms most frequently experienced by DM1 patients, either from clinician objective measures or patients self-reported measures. In particular, researcher topics mainly focus on disabilities and life-threatening conditions such as heart-respiratory defects, muscular disability, and cognitive impairment. Conversely, other disease domains, including dysphagia, digestive tract dysfunction, fatigue and pain are underrepresented in literature with regard to the frequency of patient complaints. This study emphasises that overall scientific publications topics do not fully overlap with patient needs and expectations. Our results may support stakeholders and scientists to plan studies fitting more with patient expectations.

http://dx.doi.org/10.1016/j.nmd.2018.06.418

NEXT GENERATION SEQUENCING AND EXPERIMENTAL MYOLOGY

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Next generation sequencing: new phenotype-genotype correlations

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Congenital myopathies and muscular dystrophies are clinically and genetically heterogeneous diseases with broadly overlapping features. Next generation sequencing (NGS) techniques represent a powerful tool to identify genetic variants in these disorders in contrast to classic time consuming gene by gene approach. We describe the results obtained in an extensive study of 150 genetically undiagnosed patients. The patients were classified, according to their clinical phenotype, as affected by congenital myopathy (CM), congenital muscular dystrophy (CMD), limb girdle muscle dystrophy (LGMD), distal myopathies (DM) and exercise intolerance. All the patients were followed at the French South-West Reference Center of neuromuscular disorders. The causing gene mutations could be identified in 46% of the patients. In most of the cases the variants were localized in genes classically implicated in each phenotype group (*RYR1, ACTA1, NEB* mutations in congenital myopathy group for example). However, one key finding from our study was the identification of new phenotype-genotype correlations in 10% of the cases. Two *FLNC* gene mutations in patients with congenital myopathy and severe cardiopathy; *NEB* variants in three patients with adult onset pure distal myopathy; *ACTA1* neomutation in a patient with asymptomatic elevation of creatin kinase; 11 GCG repeats expansions in *PABPN1* in a patient with predominant axial myopathy without ptosis. Of special interest is the emerging role of *TTN* gene mutations in muscular disease. We found clear pathogenic variants (compound heterozygous or homozygous stop codon, frameshift or splicing) in seven patients with quite heterogeneous clinical picture from congenital centronuclear myopathy to congenital distal arthrogryposis or limb girdle muscular weakness with cardiopathy The aim of the work is to present the global results of the study and more particularly the new phenotype-genotype correlations.

http://dx.doi.org/10.1016/j.nmd.2018.06.419

P.373

The NIH-NNDCS/CMG integrated clinico-genomic approach to undiagnosed pediatric neuromuscular patients in the NGS era

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Next-generation sequencing (NGS) approaches (multi-gene panels and whole exome sequencing (WES)) have had great impact on genetic diagnostic capabilities for inherited neuromuscular disease, frequently elucidating genetic diagnoses even in patients with less specific phenotypes by testing a large number of genes in parallel. NGS approaches also make routinely testing large genes commonly implicated in neuromuscular disease possible. However, approximately 50% of patients remain undiagnosed after use of NGS tools. The large number of variants generated using NGS leads to diagnostic uncertainty, missed diagnoses, and wrongly assigned diagnoses. Awareness of genetic mechanisms not adequately covered by exonic NGS, such as copy-neutral rearrangement, large repeat expansions, and deep intronic mutations as well as unrecognized splice and regulatory sequence variants, is also critical. To address these complex pitfalls and technical limitations, NIH-NNDCS and the Broad/MGH CMG have developed an iteratively integrated approach that draws on deep clinical phenotyping (including muscle imaging), physiological investigations, and histological analysis, in correlation with genetic data derived from WES, whole genome sequencing (WGS), and RNA sequencing from muscle, thus integrating “phenotype”, “physiotype”, “histotype”, and “genotype”. This analysis is driven by phenotype-informed targeted reanalysis of the genetic data, and plausibility assessment of genetic variants. We have shown that a correct genetic diagnosis, even when using advanced tools such as WGS and RNAseq in WES-inconclusive patients, is achieved at higher likelihood when the gene(s) to focus on is correctly predicted by phenotypic analysis. This approach also facilitates the discovery of new genes by tightly defining phenotypes allowing for cross-cohort comparison of genotypes.

http://dx.doi.org/10.1016/j.nmd.2018.06.420

P.374

Identification of gene mutations in patients with primary periodic paralysis using targeted next-generation sequencing

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Primary periodic paralysis comprises rare skeletal ion channelopathies characterized by recurrent quadriplegia typically associated with high or low serum potassium levels. We developed a gene panel that includes 10 ion channel-related genes and 245 muscular dystrophy- and myopathy-related genes and used this panel to diagnose 60 patients with primary periodic paralysis and identify the disease-causing or risk-associated gene mutations. The average sequencing depth using this panel was 488.11 ×, and the average coverage was 99.45%. Mutations in 5 genes were discovered in 40 patients (66.67%). Variants in *SCN4A, KCNJ2* and *CACNA1S* genes accounted for 92.5% of the patients with a genetic diagnosis. *SCN4A* (NM_000334) mutations accounted for the majority in this primary PP cohort (47.5%). We identified 10 *SCN4A* variants including 5 reported mutations (c.2014C>T p.Arg672Cys, c.2024G>A p.Arg675Gln, c.2111C>T p.Thr704Met, c.4352G>T p.Arg1451Leu, and c.4774A>G p.Met1592Val) and 5 novel mutations (c.107_109del p.Glu36del, c.121C>T p.Arg41Trp, c.718G>A p.Val240Met, c.3868T>C p.Phe1290Leu and c.5293G>A p.Ala1765Thr). Among them, c.2024G>A p.Arg675Gln was identified in 8 patients from 6 families as a hotspot. *KCNJ2* is the second most common genetic cause.We identified 9 reported variants (c.199C>T p.Arg67Trp, c.211G>A p.Asp71Asn, c.556C>A p.Pro186Thr, c.566G>T p.Arg189Ser, c.644G>A p.Gly215Asp, c.652C>T p.Arg218Trp, c. 899G>A p.Gly300Asp, c.919A>G p.Met307Val, and c.921G>C p.Met307Ile) in a total of 14 patients. Moreover, we identified 4 likely pathogenic variants (c.614T>A p.Phe205Tyr, c.1583G>A p.Arg528His, c.2965G>A p.Glu989Lys and c.3716G>A p.Arg1239His) in *CACNA1S* gene (NM_000069). Two *RYR1* variants (p.Glu2764Lys and p.Ala4143Val) were identified in this cohort, together with one reported *OPA1* variant (p.Ala357Thr) which is previously responsible for optic atrophy related phenotypes. Using targeted NGS, we achieved a diagnostic success rate of 66.67% in a cohort of primary PP patients. We expanded the spectrum of genotypes of primary PP and clinical phenotypes of known myopathy-related genes. We’d like to attribute this diagnostic rate to the inclusive strategy of screening for other causal factors of hypokalaemic muscle weakness and performing accurate clinical examinations and history inquiries prior to interpreting the NGS results.

http://dx.doi.org/10.1016/j.nmd.2018.06.421

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Application of next-generation sequencing using customized targeted gene panel for neuromuscular disorders in South Korea

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Next generation sequencing (NGS) has been currently known for efficient diagnostic method for diagnosing genetic disorders, including neuromuscular disorders. But, we could have a difficulty in diagnosing neuromuscular disorders, which have clinical and genetic heterogeneity. With this study, we aimed to evaluate the diagnostic yield of current targeted NGS using our customized gene panel. We developed targeted gene panels including 172 candidate genes for neuropathy panel and 213 candidate genes for muscular disorder panel. We performed NGS using customized gene panel for 102 patients with neuromuscular disorder from January 1, 2017 to February 28, 2018. According to clinical manifestation, there are several patient groups, including motor neuron disease (n=22), hereditary neuropathy (n=12), hereditary spastic paraplegia (n=10), inherited muscular disorder (n=26), idiopathic hyperCKemia (n=4), channelopathy (n=7), and the rest of patients. We identified 22 patients (22.5%) with genetic confirmation using targeted NGS. 19 patients had pathogenic or likely pathogenic SNVs in 14 genes, including *SPAST* (n=3), *DYSF* (n=3), *TTN* (n=2), *DMD, GNE, SCN4A, FUS, KIF5A*,

MUSK, *DNAJB6, MYH3, CACNA1S, GJB1, ABCD1* (n=1). 3 patients had pathogenic or likely pathogenic CNVs (1 duplication and 1 deletion of *PMP*, exon 9-16 duplication of *SPAST*). After NGS testing, the other 2 patients were diagnosed as myotonic muscular dystrophy type 1 with increased CTG repeat of *DMPK*, and spinal and bulbar muscular atrophy with increased CAG repeat of *AR*, respectively. NGS using customized gene panel is useful for diagnosis of neuromuscular disorder when we diagnosed the specific disease. We can increase the efficacy of NGS with specific criteria for NGS and standardization of diagnostic approach.

http://dx.doi.org/10.1016/j.nmd.2018.06.422

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International DMD: a project devoted to dystrophin mutation identification by NGS technology in eastern Europe and northern African countries

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Extensive molecular diagnosis in genetic diseases is vital to confirm clinical diagnosis and to enable genetic counseling and personalized management. Duchenne muscular dystrophy (DMD) is a rare genetic neuromuscular disease affecting 1 in 5.000 male births worldwide, due to a variety of dystrophin gene mutations. Since 2016, PTC Therapeutics International Ltd. and the University of Ferrara, Italy, have established a collaboration focused on identifying patients affected by rare genetic disorders through increased genetic testing activities, with an initial focus on DMD. Genetic testing is available to patients throughout European countries and other regions. Diagnostic settings include MLPA (MRC-Holland) and NGS dystrophin gene sequencing (Multiplicom). Currently, DNAs from Poland (50), Hungary (17), Lituania (6), Romania (7), Russia (1), Bosnia (4), Croatia (2) Bulgaria (13) Cyprus (2), Ucraina (1) and Algeria (40) were collected for a total of 143 samples. Analyses have been completed in 125 patients. MLPA screening identified 35 samples with large deletions/duplications, while NGS analysis identified 31 nonsense, 15 small del/dup, 15 splice site and 3 missense mutations. Twenty-six (26) patients were negative for both MLPA and NGS analyses, suggesting the presence of atypical mutations. Notably, among the small mutations identified so far (64), 50% are nonsense and 25% are canonical splice site mutations. The early identification of the underlying genetic mutation is critical for the standard of care including treatment choice and eligibility for clinical trials. Genetic counselling can also be offered to patients and families via a telegenetics service (www.ospfe.it/medicalgenetics).

http://dx.doi.org/10.1016/j.nmd.2018.06.423

P.377

The latin America experience with a next generation sequencing genetic panel for recessive limb-girdle muscular weakness

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Limb-girdle muscular dystrophy (LGMD) is a group of neuromuscular disorders of heterogeneous genetic etiology with more than 30 directly related genes. LGMD is characterized by progressive muscle weakness involving the shoulder and pelvic girdles. An important differential diagnosis among patients presenting with proximal muscle weakness (PMW) is late-onset Pompe disease (LOPD), a rare neuromuscular glycogen storage disorder, which typically presents with respiratory insufficiency in addition to PMW. Patients with PMW, with or without respiratory symptoms, were included in this study to evaluate the profile of variants for the included genes related to LGMD and LOPD and the frequency of variants in each gene among the patient population. Over 20 institutions across Latin America (Brazil, Argentina, Peru, Ecuador, Mexico, Chile) enrolled 2103 individuals during 2016 and 2017. Dried blood spots were collected from patients and sent to the laboratory. Nine autosomal recessive LGMDs and Pompe disease were investigated in a 10-gene panel (*ANO5, CAPN3*, *DYSF, FKRP, GAA, SGCA, SGCB, SGCD, SGCG, TCAP*), based on reported disease frequency in Latin America. Sequencing was performed with Illumina's NextSeq500 and variants were classified according to ACMG guidelines; pathogenic and likely pathogenic treated as one category (P) and variants of unknown significance (VUS) will be described. This panel yielded a total of 1304 variants (246 homozygous, 234 two heterozygous variants in the same gene, and 56 one heterozygous). The gene with the highest number of variants was *DYSF*, with 496 variants (213 P, 283 VUS), followed by *CAPN3* (254; 162 P, 92 VUS), *GAA* (126; 52 P, 74 VUS), *ANO5* (119; 46 P, 73 VUS), SGCA (110; 67 P, 43 VUS), *FKRP* (80; 45 P, 35 VUS), *SGCG* (34; 14 P, 20 VUS), *SGCB* (31; 15 P, 16 VUS), *TCAP* (30; 15 P, 15 VUS) and *SGCD* (24; 5 P, 19 VUS). These results show the importance of the inclusion of *GAA* for the investigation of patients with PMW.

http://dx.doi.org/10.1016/j.nmd.2018.06.424

P.378

Clinical nonsense mutations in neuromuscular disorders

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Nonsense mutations (NM) are single base substitutions that introduce a premature stop codon. There are 5218 single gene disorders and traits (OMIM), and neuromuscular disorders (NMD) represent ~ 9% of all known Mendelian phenotypes. We present the most frequent NM that produce an NMD, in the clinical realm; as an initial step to analyze the potential benefit of emerging nonsense readthrough therapies. Accessing the free-open-database of ClinVar, a tool to facilitate the evaluation of variation-phenotype relationships, we were able to download data submitted by 17 different laboratories offering diagnostic testing for clinical purposes, across NA and Europe, which were trusted and major contributors to ClinVar. We collected only "Clinical" and "nonsense mutations" obtaining 10426 different mutations of 1094 genes, of which 1022 were likely pathogenic/pathogenic and 7821 pathogenic. Excluding oncogenes, there are 5736 NM in 1044 different monogenic disease (MD) genes. One thousand and fifty-five different variations of 96 genes were related to a NMD phenotype representing the 18.4% of all NM that can cause a MD. The most frequent NMD with an NM were *TTN* related phenotypes (256 mutations, representing 4.4% of all NM), and *DMD* (234 mutations, representing 4% of all NM). Other frequent NM and NMD phenotype were: *DYSF, MTM1*, and *LMNA*. We also classify the disease severity ranging from lethal to chronic progressive. The data obtained in this analysis represents real-world clinical information which we can use to understand the potential impact of an efficient nonsense mutation read-through agent.

http://dx.doi.org/10.1016/j.nmd.2018.06.425

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Transcriptome analysis of trans-differentiated myotubes for the diagnosis of neuromuscular disorders

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Gene panel and whole exome analyses remain the mainstream methods of variant and gene discovery in patients with Mendelian diseases. The analyses of patient's whole genome and transcriptome allow to explore additional classes of variants and functional properties of patient's tissue, leading to the improvement of the diagnostic rate. Here, we report the integrative analysis of 73 transcriptomes, sampled from fibroblast tissue, skeletal muscle, and *in vitro* trans-differentiated myotubes (t-myotubes) of patients with neuromuscular disorders. Our analysis includes variant discovery, expression outliers, and pathogenic splice changes. We show that for the most genes relevant to muscular diseases, the analysis of t-myotubes allow to discover variants and splice changes similarly to the muscular tissue. We conclude, that the integrative analysis of the transcriptome of t-myotubes in the first place could become a reliable alternative to the currently genetic diagnostic algorithm.

http://dx.doi.org/10.1016/j.nmd.2018.06.426

P.380

The complexity of splicing pattern in human adult skeletal muscles: a key to understanding genotype-phenotype correlations

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Most multi-exonic genes undergo tissue specific alternative splicing events (ASEs). Similarly, ASEs are often dependent on developmental stage. The splicing regulation of specific transcripts seems to be part of a large and complex process causing multiple physical and functional consequences. For example, differential splicing can modulate protein-protein interactions and, similarly, can affect the protein length modifying its structural and functional properties. We performed a RNA-Sequencing experiment on 42 human biopsies collected from 12 anatomically different skeletal muscles of 11 individuals without any muscle disorders in order to map ASEs in adult human skeletal muscles. Some of the largest human genes have a high expression level in skeletal muscles. One example is the 364-exon *TTN* gene encoding titin, a giant protein with multiple functions in skeletal and cardiac muscles. Because of alternative splicing, several titin isoforms are expressed. With over 1 million potential splicing variants, *TTN* is virtually the most alternatively spliced human gene. We have identified a large number of these ASEs, providing the first RNA-Seq-based picture of *TTN* splicing pattern in adult human skeletal muscle. Moreover, by using PAC-BIO, a long-read sequencing technology, we mapped several ASEs along the some molecule. The same approach shows similar complex splicing patterns for other muscle transcripts and also reveals previously unreported exons in well-known muscle disease genes. A refinement of the expression profiling in different muscular tissues (heart and skeletal muscles) and/or different pathological and physiological states (e.g., fetal *versus* adult) would further improve our understanding of genotype-phenotype correlations.

http://dx.doi.org/10.1016/j.nmd.2018.06.427

P.381

Muscle satellite cells and impaired late stage regeneration in different murine models of muscular dystrophies

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Satellite cells (SCs) are the main stem cells of the muscle, responsible for its regenerative capacity after injury. In muscular dystrophies, SCs are constantly activated, but a failure of the regenerative process results in muscle degeneration and weakness. We studied muscle SCs in three mouse dystrophic strains: DMDmdx, Largemyd, DMDmdx/Largemyd, to evaluate SCs behavior in muscles with different degrees of degeneration. The dystrophic muscles from the three strains showed similar results, retaining satellite cells pool, expressing PAX7, an important muscle factor for self-renewal of the SCs pool. In addition, a high proportion of proliferating cells was observed by the analysis of cell cycle markers. Expression analysis demonstrated that the cascade of regeneration genes was also activated in all the dystrophic muscles, with high levels of MYOD and Myogenin. The ability to form new fibers was also preserved, with the presence of a significant number of new fibers expressing dMHC. However, these new fibers show incomplete maturation characteristics, such as small size and no variation in fiber caliber, which could be determinant for its dysfunction. On the other hand, muscle degeneration was intense, with significant more connective tissue infiltration in dystrophic mice. We concluded that dystrophic muscles, independently of the degree of degeneration, retain the pool of satellite cells with proliferating capacity and ready to respond to regenerating stimuli. However, the maturation of these new fibers is incomplete and do not prevent the degeneration of the muscle. Effort to improve late muscle regeneration should better contribute to therapeutic approaches.

http://dx.doi.org/10.1016/j.nmd.2018.06.428

P.382

Klf5 has essential roles in myoblast differentiation and survival during fetal muscle development

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Klf5, a zinc-finger transcription factor of the Kruppel-like factor family, regulates cell proliferation, differentiation and apoptosis during development and in certain disease states, such as cancer. Recently, we have reported that Klf5 is an essential regulator of skeletal muscle differentiation and regeneration, acting in concert with myogenic transcription factors such as MyoD and Mef2 [1]. In this study, we focused on the functions of Klf5 during muscle development. We performed in situ hybridization and immunostaining for Klf5 with E10.5 murine embryos and found that Klf5 is expressed in the myotome and co-localized with myogenin. To assess the functions of Klf5 during embryogenesis, we generated Pax3Cre/+;Klf5flox/flox (Klf5cKO) embryos in which Klf5 is deleted in the muscle progenitor cells. Analysis of E11.5 Klf5cKO embryos revealed no obvious defects in migration of muscle progenitor cells or somite development compared with Klf5flox/flox control embryos. However, loss of Klf5 led to impairment of the development of hindlimb muscles and diaphragm at E18.5. As a result, most of the Klf5cKO neonates died at P0 because of the respiratory failure. Myoblasts from survived Klf5cKO mice showed decrease of Myod1 and myogenin expression during differentiation compared with the control cells. In addition, Klf5cKO myoblasts exhibited a defect of myotube formation. We also observed that deletion of Klf5 induced apoptosis in myobasts, and exogenous Klf5 could partially rescue the defect of myotube formation. Our results suggest Klf5 is required for the fetal muscle development via myoblast differentiation and survival. These findings provide new insight into the molecular mechanisms of muscle differentiation, which informs development of stem-cell-based therapies for muscle diseases such as muscular dystrophies and sarcopenia.

http://dx.doi.org/10.1016/j.nmd.2018.06.429

P.383

Cullin-3 is required for normal skeletal muscle development

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E3-ubiquitin ligases are protein complexes that are essential for the recognition and the degradation of specific substrates by the ubiquitin-proteasome pathway. Cullin-RING ligases represent the largest E3-ubiquitin ligase family in mammals. The Cullins constitute the backbone of the E3-ubiquitin ligase complex, and interact with specific substrate adaptors that are necessary for

the recruitment of their individual substrates for degradation. While roles for Cullin-RING ligases were intensively studied in the context of cancer, very little is known about their functions in muscle biology. Recently, several genes of the BTB-domain family (*KBTBD13*, *KLHL40* and KLHL41) were found mutated in severe and early onset forms of nemaline myopathy. Due to their BTB-domains, these proteins are thought to be substrate adaptors for Cullin-3. These findings argue in favor of important and yet largely uncharacterized roles for Cullin-3 mediated protein turnover for muscle development, maintenance and function. We demonstrated that Cullin-RING ligase function is essential for myogenesis *in vitro* through the use of MLN4924, an inhibitor of neddylation. However, the role of Cullin-3 in muscle development remains poorly understood. Using conditional knockout mice for Cullin-3 in skeletal muscles, we demonstrate the pivotal role of this protein for postnatal life. Our data reveal that absence of Cullin-3 leads to respiratory defects at birth, associated with a strong skeletal muscle atrophy and neuromuscular junction disorganization. Large-scale proteome analysis of embryonic muscles revealed that lack of Cullin-3 results in the accumulation of muscle specific and cytoskeletal proteins, presumably representing novel substrates of this E3-ligase. Our results demonstrate that Cullin-3 mediated protein turnover is required for proper early skeletal muscle development. We are currently investigating the molecular mechanisms that contribute to the severe myopathy observed in these animals.

http://dx.doi.org/10.1016/j.nmd.2018.06.430

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RNAseq in urine-derived stem cells identified the expression of 308 neuromuscular gene transcripts

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We have previously demonstrated that native and differentiated urine stem cells (USCs) are able to recapitulate the DMD cell phenotype. In this study we analyzed the transcriptome of wild type native USCs in order to propose them as an *in vitro* model for studying other neuromuscular disorders. The expression of 472 genes involved in 16 groups of neuromuscular diseases (http://www.musclegenetable.fr/) was investigated by RNAseq analysis. Studied USCs were isolated from 3 healthy subjects (males). We found that 308 and 310 out of 472 neuromuscular explored genes are well expressed. Transcripts related to vast majority of disease groups are represented with different expression rate, with the exception of ion channel and malignant hyperthermia genes. 70 to 90% of genes causing hereditary neuropathies, motor neuron diseases, metabolic myopathies, hereditary paraplegias, muscular and congenital muscular dystrophies, are expressed. 30-60% of the causative genes are detected in the remaining neuromuscular disease groups. RNAseq analysis also identified novel isoforms or splicing choices, and many new transcripts were identified. Our results suggest that USCs represent an appealing tool to study transcriptome in several NMD types; the high number of NMD expressed genes makes them eligible also for mutation detection and for diagnostic purposes. UCSs might also represent surrogate cells to explore mutation consequences on RNA, as splicing variations or atypical mutations affecting RNA processing. Drug screening and biomarkers validation might also be attracting studies to be carried out in these cells.

http://dx.doi.org/10.1016/j.nmd.2018.06.431

P.385

Physician-Level muscle disease classifier for computer-aided diagnostics with neural networks

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Even in the current era of molecular biology, muscle pathology still plays a central role in diagnosing muscle disease. Among these diseases, muscular dystrophy (MD) is a group of progressive hereditary muscle diseases for which no curative therapy is available, and immune-mediated necrotizing myopathy (IMNM) is a subclass of myositis that can be treated by immune therapy. Whereas MD and IMNM are both pathologically characterized by the presence of necrotic and regenerating fibers and often look similar. Therefore, the differentiation of these conditions is a hot topic in myology. To develop and evaluate an algorithm for computer-aided muscle histopathological diagnosis that uses deep learning. We chose two disease categories, MD and IMNM, and aimed to distinguish between these conditions. We prepared 11-layer convolutional neural networks and 1977 (MD: 885, IMNM: 1092) H&E-stained muscle section images classified in real diagnosis. Of these, 190 (MD: 78, IMNM: 112) images were used as a test set and the others (MD: 807, IMNM: 980) for training. After training our model with the training dataset, we evaluated its classification performance. For comparison, seven physicians also classified the same test set. After training of the model, the AUC, the area under the ROC (Receiver operating characteristic) curve, of our model was 0.94. In terms of accuracy, the classifier achieved better results, 88% on average, than seven physicians specializing in muscle disease among whom the best accuracy was 78%, indicating that our model outperforms physicians at classifying the two muscle diseases on H&E images. There are a number of limitations in this study. For example, we used only H&E images and the classification (diagnosis) was made between only two disease conditions. Nevertheless, our results suggest the deep neural network model can make pathological diagnosis better than physicians at least under certain conditions.

http://dx.doi.org/10.1016/j.nmd.2018.06.432

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A versatile, modular digital script for automated high-throughput multiparametric myofibre analysis in brightfield and epifluorescent paradigms

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Digital scripts are vital for unbiased, high-throughput multiparametric analysis of muscle landscapes in frozen/fixed histology sections with useful diagnostic and research applications. We have developed a series of image analysis methods with Definiens Tissue Studio and Developer, applicable to digital scans of entire sections of skeletal muscle (chromogenic/fluorescent stained), and tailored specifically to neuromuscular applications. Initially the script was developed for global landscape assessment, resolution then increased by achieving fibre separation for population analysis, and current method development is making use of multiplexed staining to investigate subpopulations of fibres. The global analysis mapped oxidative changes in the mixed fibre-type gastrocnemius muscle, with COX-SDH staining, in a long-term rodent model of critical illness and recovery. Staining intensity translated to digital heatmaps as surrogate indicators of mitochondrial biogenesis. Initial analysis at the single fibre level was problematic due to lack of boundary definition, highlighting the importance of using an ubiquitiously expressed membrane marker (spectrin/laminin), introduced in subsequent analyses, to create a 'mask' for defining the sarcolemma of each myofibre. Brightfield analysis of muscle fibre diameter in 'histologically normal' paediatric muscle biopsies provided good correlation between whole section counts and manually selected transverse regions, providing age-stratified data on muscle fibre size. In fluorescent stained sections, a key feature of the script is background normalisation for maximising signal: noise ratio. Techniques used include a moving average method and thresholding based on a global average of background signal. Current modules measure numerous indices related to the level of expression of markers, and the coverage of markers above a given threshold. This technique was applied to quantify dystrophin expression in transverse sections from Duchenne muscular dystrophy biopsies. Further script development relates to the analysis of additional markers in sec-

tions with three or more multiplexed stains. In conclusion, our unique modular approach allows for continuous machine learning, increasing the script's capacity to generate a variety of high-throughput qualitative and quantitative datasets with a wide range of neuromuscular applications.

http://dx.doi.org/10.1016/j.nmd.2018.06.433

P.387

Nonsense mutation induced exon skipping in Becker muscular dystrophy

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Duchenne muscular dystrophy is caused by frame-shift or nonsense mutation in the DMD gene, while its milder form, Becker muscular dystrophy (BMD) by in-frame deletion/duplication or missense mutations. Puzzlingly, however, some patients with nonsense mutation are known to show BMD phenotypes and its mechanism is attributed to the skipping of the exon containing the nonsense mutation, resulting in in-frame deletion. Nevertheless, there were only a few reports describing such cases. To clarify molecular consequences of nonsense mutations in the DMD gene in a large cohort of Japanese BMD patients. Among 1497 dystrophinopathy patients in our cohort, 17 had a nonsense mutation but showed faint-and-patchy dystrophin expression pattern on muscle immunohistochemistry. In silico prediction for exonic splicing enhancer was performed on all the nonsense mutations of the 17 patients. We performed western-blot and mRNA analyses to evaluate the expression level of the splicing products. We further quantitate the skipping rate by using hybrid minigene plasmid H492. Skipping of the exon harboring nonsense mutation was observed in 7 of the 10 patients examined. Hybrid minigene analysis confirmed these skipping. These 7 nonsense mutations gave high scores for occurrences of skipping by in silico prediction. Reversed correlation was seen between skipping rate and phenotypic severity. Exon skipping events can be attributed to dystrophin expression in the majority of cases with nonsense mutation and dystrophin positive staining. Nevertheless, skipping of nonsense-containing exon is not observed in some cases, indicating the necessity to clarify the as-yet-known mechanism by other methods such as RNA-seq. The presence of BMD patients who have nonsense mutations and dystrophin expression, gives a mystery of apparent genotype-phenotype discrepancy. Our results give an explanation to the reason for the milder phenotypes associated with nonsense mutations in the *DMD* gene at the molecular level in the majority, albeit not all, of the patients.

http://dx.doi.org/10.1016/j.nmd.2018.06.434

Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 28 (2018) S195–S212

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https://doi.org/10.1016/j.nmd.2018.06.018
0960-8966

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- A minimum of 50 Fellowships (of 1000 Euros) are available from the WMS Education Fund.
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- The President's Prize for the best presentation by a 'young' first-timer (500 Euros)
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For more information on the above and to catch up with news and activities of the WMS including some great photo galleries from past congresses please visit the website: http://worldmusclesociety.org

Haluk Topaloğlu
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24th INTERNATIONAL CONGRESS OF THE
WORLD MUSCLE SOCIETY

1st- 5th October 2019 – Copenhagen, Denmark

A 4-day Symposium of the World Muscle Society (WMS) in association with its official journal Neuromuscular Disorders

The symposium will be held in the traditional WMS format with 3 selected topics:

- **Metabolic disturbances in neuromuscular diseases**
- **Extra-muscular manifestations of neuromuscular diseases**
- **Advances in the treatment of neuromuscular disorders**

Contributions will also be welcome on new advances across the neuromuscular field.

One day of the symposium will be dedicated to each of the selected topics. Invited keynote speakers will summarize the state of the art on the selected topics, covering clinical, molecular and other aspects. The sessions will comprise selected oral papers and poster presentations with guided discussions.

Venue: Tivoli Gardens, Copenhagen, Denmark

Local Organiser:

John Vissing, National Hospital, Rigshopsitalet, *Copenhagen*

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Registration and Abstract Submission opening tbc
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Join us for the opening reception held on Tuesday 1st October in the theatre, Det Ny Teater, located a 5-minute walk from Tivoli gardens. The meeting will follow the long tradition of WMS to facilitate networking and catch up on the latest developments in myology around the world during this 4-day meeting.

The congress venue, Tivoli, is the world's oldest amusement park with a beautiful garden. Tivoli will be closed to the public while WMS is taking place. The venue has very easy access to hotels and the airport, which is only 20 minutes away by train or metro. The Copenhagen Neuromuscular Center at the National Hospital, Rigshospitalet, led by John Vissing, will host and organise this meeting. Contributions about new advances across the neuromuscular field are very welcome. The main thematic topics that will be addressed in the plenary sessions will be:

Main topics:

Metabolic disturbances in neuromuscular diseases

Extra-muscular manifestations of neuromuscular diseases

Advances in the treatment of neuromuscular disorders

Contributions will also be welcome on new advances across the neuromuscular field.

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