

ACTA MYOLOGICA

(Myopathies, Cardiomyopathies and Neuromyopathies)

Vol. XL - December 2021 (SUPPL. 1)

Official Journal of
Mediterranean Society of Myology
and
Associazione Italiana di Miologia

Founders: Giovanni Nigro and Lucia Ines Comi

Three-monthly

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Established in 1982 as *Cardiomyology*

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Acta Myologica publishes 4 issues per year in March, June, September, December. The Journal is available in OPEN ACCESS at: www.actamyologica.it

Acta Myologica is cited in Index Medicus, PubMed/MedLine, Scopus, Open-J Gate, Free Medical Journals, Socolar. The Journal is available on PubMed Central (<http://www.ncbi.nlm.nih.gov/pmc/journals/1221/>).

Journal Citation Reports: SJR 2019 0.616; SNIP 2019 0.818
Acta Myologica is available on Google Scholar

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Tribunal Authorization, Napoli N. 3827, January 10, 1989 - Journal registered at "Registro pubblico degli Operatori della Comunicazione" (Pacini Editore srl registration n. 6269 - 29/8/2001).

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Publisher

Pacini
Editore

Via A. Gherardesca - 56121 Pisa, Italy

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Published by Pacini Editore Srl, Pisa, Italy, December 2021

DOI:10.36185/2532-1900-056

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OF THE ITALIAN ASSOCIATION OF MYOLOGY**

Digital Edition

December 01-04, 2021



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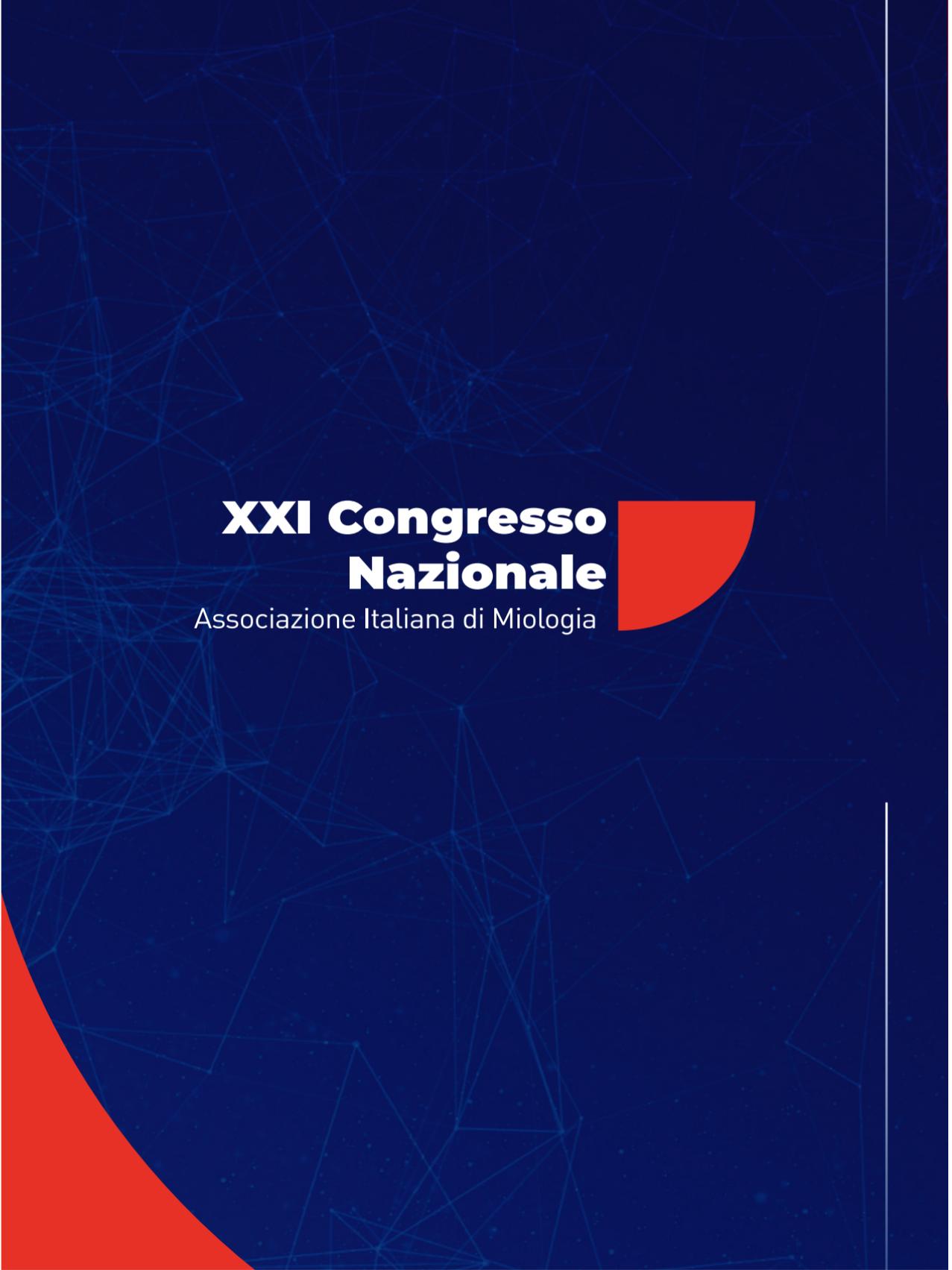
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INDICE

pag. 5 | Consiglio Direttivo AIM
7 | Faculty

pag. 8 | Programme at a glance

PROGRAMME

pag. 13 | Wednesday, 1st December
13 | Thursday, 2nd December
16 | Friday, 3rd December
20 | Saturday, 4th December

pag. 23 | Poster session

INFORMAZIONI UTILI

pag. 28 | Informazioni generali
28 | Requisiti ottenimento crediti formativi ECM



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PROGRAMME AT A GLANCE

Wednesday, 1st December 2021

14.00	Conference opening
14.10 - 14.30	Introduction
14.30 - 16.20	Workshop 1: Neuromuscular diseases during and after the COVID-19 Pandemic
16.20 - 17.20	Round Table: New nomenclature for LGMD. Is it exhaustive? New nomenclature for LGMD. Is it exhaustive?
17.20 - 18.50	Workshop 2 – Basic Muscle Research

Thursday, 2nd December 2021

08.00 - 09.00	Early Morning Seminar: Therapies for Myasthenia Gravis and Myasthenic Syndromes
09.00 - 10.40	Workshop 3: New treatment approaches for neuromuscular diseases
10.40 - 12.40	Symposium: Update of Pharmacological Treatment of SMA
12.40 - 13.10	Hot Topics
14.00 - 15.15	ORAL COMMUNICATIONS 1: New treatments for SMA
17.00 - 18.45	ORAL COMMUNICATIONS 2 - Myopathies and muscular dystrophies: new phenotypes, biomarkers, and therapies – 1

PROGRAMME AT A GLANCE

15.15 – 17.00	Poster session (Sessione non accreditata ECM)	
	CH. 1 Dystrophinopathies and muscular dystrophies	CH. 2 Myasthenia, inflammatory myopathies, channelopathies
	CH. 3 Myopathies	CH. 4 SMA and motor neuron disorders
17.00 - 18.45	ORAL COMMUNICATIONS 2 - Myopathies and muscular dystrophies: new phenotypes, biomarkers, and therapies – 1	
Friday, 3 rd December 2021		
08.00 - 08.40	Early Symposium: Myotubular Myopathy (MTM)	
08.40 - 10.00	Workshop 4 - Update on mitochondrial disease	
10.00 - 10.30	Invited Lecture: Latest developments in Facioscapulohumeral Dystrophy	
10.30 - 11.30	Workshop 5 - Inflammatory myopathies	
11.30 - 12.00	Invited Lecture “Recent update on dermatomyositis”	
12.00 - 13.00	Symposium - Patient assessment in view of new treatments for Pompe disease	
14.00 – 15.30	ORAL COMMUNICATIONS 3 Myopathies and muscular dystrophies: new phenomic, genomic, and pathogenetic aspects	

XXI Congresso Nazionale

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PROGRAMME AT GLANCE

Friday, 3rd December 2021

15.30 - 17.15	ORAL COMMUNICATIONS 4 Natural history and new diagnostic tools in neuromuscular disorders
17.15 - 18.45	ORAL COMMUNICATIONS 5 Myopathies and muscular dystrophies: new phenotypes, biomarkers, and therapies – 2

Saturday, 4th December 2021

08.30 – 09.30	Wake up Muscle Club
09.30 – 11.00	Workshop 6 - Next generation molecular diagnostics
11.00 - 12.30	AIM meets Patients and Family Association
12.30	Awards Ceremony for the best works
13.00	Conclusions



**XXI Congresso
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Associazione Italiana di Miologia

PROGRAMME

Wednesday, 1st December 2021

14.00 | Conference opening

Greetings from the Authorities and introduction of the AIM President

14.30 - 16.20 | Workshop 1:

Neuromuscular diseases during and after the COVID-19 Pandemic

Chairmen: *Giacomo Comi - Rocco Liguori*

- Muscular complications | *Delia Gagliardi*
- Peripheral nerve complications | *Massimiliano Filosto*
- Neuromuscular plate junction complications | *Rocco Liguori*
- Telemedicine and patient follow-up | *Giulia Ricci*
- Territorial management of neuromuscular patients | *Antonio Trabacca*

16.20 - 17.20 | Round Table

New nomenclature for LGMD. Is it exhaustive?

Chairman: *Corrado Angelini*

Participants: *Giacomo Comi, Carlo Minetti, Elena Pegoraro, Vincenzo Nigro, Antonio Toscano*

17.20 - 18.50 | Workshop 2

Basic Muscle Research

Chairmen: *Elena Pegoraro, Claudio Bruno*

- Muscle homeostasis and regeneration: from cellular and molecular mechanisms to therapeutic opportunities | *Antonio Musarò*
- SMA molecular pathogenesis downstream of the SMN1 gene | *Stefania Corti*
- The alarmin HMGB1 links oxidative stress and inflammation in muscular dystrophy | *Emilie Venereau*
- Mechanical-metabolic dysfunction in muscle disorders: new insights and therapeutic implications | *Annamaria De Luca*

Thursday, 2nd December 2021

08.00 - 09.00 | Early Morning Seminar:

Therapies for Myasthenia Gravis and Myasthenic Syndromes

Chairman: *Antonio Di Muzio*

- Atypical clinical Phenotypes | *Carmelo Rodolico*
- Focus on complex patients in Myasthenia gravis | *Amelia Evoli*
- New Therapeutical approaches in Myasthenia | *Renato Mantegazza*

09.00 - 10.40 | Workshop 3**New treatment approaches for neuromuscular diseases****Chairmen:** *Gabriele Siciliano, Maurizio Moggio*

- Molecular therapy in muscular dystrophy | *Stefano Previtali*
- Long-term effects of innovative treatments in DMD/BMD | *Luca Bello*
- Myotonia and channelopathies | *Lorenzo Maggi*
- Old and New Steroids influence in Muscular Dystrophies | *Michela Guglieri*
- A gene therapy approach in Pompe Disease | *Federico Mingozzi*

10.40 - 12.40 | Symposium**Update of Pharmacological Treatment of SMA****Section 1****Chairman:** *Enrico Bertini*

- What we know, don't know, and suspect about SMN function | *Fabrizio Gardoni*
- Modulating the levels of SMN beyond neurons: possible implications for clinical practice | *Valeria Sansone*

Section 2**Chairman:** *Eugenio Mercuri*

- New perspectives in SMA Type 1 | *Adele D'Amico*
- New perspectives in later onset SMA | *Giacomo Comi*

Section 3**Chairman:** *Claudio Bruno*

- Gene therapy in clinical trials | *Eugenio Mercuri*
- Beyond clinical trials: the Italian experience | *Emilio Albamonte*

12.40 - 13.10 | Hot Topics:**Chairman:** *Antonella Pini*Neonatal screening in neuromuscular disorders - *Francesco Danilo Tiziano*Early diagnosis of neuromuscular diseases - *Alice Donati***14.00 - 15.15 | ORAL COMMUNICATIONS 1:****New treatments for SMA****Chairmen:** *Serenella Servidei, Roberto Massa***14.00 - 14.15 | Clinical and demographic features of patients with SMA on treatment with risdiplam: the iSMAC experience.**

E. Albamonte, G. Coratti, F. Salmin, A. Zanolini, M. Pane, MC Pera, D. Leone, L. Antonaci, A. D'Amico, M. Catteruccia, E. Bertini, C. Bruno, N. Brolatti, S. Messina, M. Sframeli, R. Piras, E. Mercuri, VA Sansone
(Milano; Roma; Genova; Messina)

14.15 - 14.30 | Amifampridine safety and efficacy in ambulatory SMA Type 3 patients: a randomized, placebo-controlled, crossover, phase 2 trial

S. Bonanno, R. Giossi, R. Zanin, V. Porcelli, G. Ingenito, Z. Stevic, S. Peric, L. Maggi (Milano; Belgrade, Serbia)

- 14.30 - 14.45 | FIREFISH Part 2: 24-month efficacy and safety of risdiplam in infants with Type 1 spinal muscular atrophy (SMA)**
B.T. Darras, R. Masson, M. Mazurkiewicz-Beldzinska, K. Rose, H. Xiong, E. Zanoteli, G. Baranello, C. Bruno, D. Vlodavets, A. Dodman, M. El-Khairi, M. Gerber, K. Gorni, H. Kletzl, R. S Scalco, L. Servais
(Boston, MA, USA; Milan, Italy; Gdansk, Poland; Sydney, Australia; Beijing, China; São Paulo, Brazil; London, UK; Genoa, Italy; Moscow, Russia; Basel, Switzerland; Welwyn Garden City, UK; Basel, Switzerland; Oxford, UK; Liège, Belgium; Paris, France)
- 14.45 - 15.00 | Long-term nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3**
L. Maggi, L. Bello, S. Bonanno, A. Govoni, C. Caponnetto, S.G. Grisanti, L. Passamano, M. Grandis, G. Nicocia, F. Trojsi, F. Cerri, A. Gardani, B. Risi, G. Giulio, M. Ferraro, V. Bozzoni, L. Caumo, R. Piras, R. Tanel, E. Saccani, M. Meneri, V. Vacchiano, G. Ricci, G. Sorarù, E. D'Errico, M.A. Maioli, I. Tramacere, S. Bortolani, G. Pavesi, R. Zanin, M. Silvestrini, L. Politano, A. Schenone, S. C. Previtali, A. Berardinelli, M. Turri, L. Verriello, M. Coccia, R. Mantegazza, R. Liguori, M. Filosto, G. Marrosu, G. Siciliano, I. L. Simone, T. Mongini, G.P. Comi, E. Pegoraro
(Milano; Padova; Pisa; Genova; Napoli; Pavia; Brescia; Torino; Carbonia; Trento; Parma; Bologna; Bari; Cagliari; Ancona; Bolzano)
- 15.00 - 15.15 | Onasemnogene abeparvovec palliative care experiences and challenges in type 1 Spinal Muscular Atrophy: the oldest care for the newest drug?**
A. Mercante, G. Perilongo, E. Salamon, A. Santini, F. Benini, C. Agosto (Padova)
- 15.15 - 17.00 | Poster session (Sessione non accreditata ECM)**
CHANNEL 1 - Dystrophinopathies and muscular dystrophies
 Chairmen: *Luca Bello, Adele D'Amico*
- CHANNEL 2 - Myasthenia, inflammatory myopathies, channelopathies**
 Chairmen: *Carmelo Rodolico, Matteo Garibaldi*
- CHANNEL 3 - Myopathies**
 Chairmen: *Enzo Ricci, Lorenzo Maggi*
- CHANNEL 4 - SMA and motor neuron disorders**
 Chairmen: *Antonio Di Muzio, Tiziana Mongini*
- 17.00 - 18.45 | ORAL COMMUNICATIONS 2**
Myopathies and muscular dystrophies: new phenotypes, biomarkers, and therapies – 1
 Chairmen: *Francesca Magri, Rita Barresi*
- 17.00 - 17.15 | Myalgia and fatigue as long term symptoms in COVID-19 patients: a 1-year follow up**
S. Cotti Piccinelli, A. Pilotto, V. Cristillo, F. Schiano di Cola, B. Risi, G. Bonzi, M. Mazzola, M. Filosto, A. Padovani (Brescia)

- 17.15 - 17.30 | Phenotypic spectrum of IGHMBP2 gene mutations and natural history study in a cohort of European patients**
A. Govoni, A. Nuredini, M. Taiana, M. Nizzardo, A. D'Amico, E. Bertini, V. Sansone, E. Albamonte, S. Messina, F. Mari, E. Cesaroni, L. Porfiri, D. Tiziano, G.L. Vita, M. Sframeli, E. Merico, E. Schirinzi, G. Siciliano, J. A. F. Ramos, I. Ostrowska, M. Piontek, G.P. Comi, S. P. Corti
(Milano; Roma; Messina; Firenze; Ancona; Pisa; Cordoba, Spain; Szczecin, Poland; Zabrze, Poland)
- 17.30 - 17.45 | ASPIRO Gene Therapy Trial In X-Linked Myotubular Myopathy (XLMTM): Update on Preliminary Efficacy and Safety Findings**
W. Miller, P. B. Shieh, N. Kuntz, J. J. Dowling, W. Müller-Felber, A. Blaschek, C. G. Bönnemann, A. R. Foley, D. N. Saade, A. M. Seferian, L. Servais, M. W. Lawlor, M. Noursalehi, S. Prasad, S. Rico
(San Francisco, CA, USA; Los Angeles, CA, USA; Chicago, IL, USA; Toronto, ON, Canada; Munich, Germany; Bethesda, MD, USA; Paris, France; Oxford, UK; Milwaukee, WI, USA)
- 17.45 - 18.00 | Safety, β -Sarcoglycan Expression, and Functional Outcomes From Systemic Gene Transfer of rAAVrh74.MHCK7.hSGCB in LGMD2E/R4**
L. R. Rodino-Klapac, E. R. Pozsgai, S. Lewis, D. A. Griffin, A. S. Meadows, K. J. Lehman, K. Church, N. F. Reash, M. A. Iammarino, B. Powers, L. N. Alfano, L. P. Lowes, E. Koenig, S. Neuhaus, X. Li, L. Picaro, J. R. Mendell
(Cambridge, MA, USA; Columbus, OH, USA)
- 18.00 - 18.15 | An integrated and multiparametric system to identify diagnostic and prognostic parameters in neuromuscular diseases towards trials readiness.**
G. Ricci, A. Tonacci, F. Torri, G. Aringhieri, F. Sansone, A. Rubegni, G. Siciliano, F. M. Santorelli, R. Conte and The InGene 2.0 project Consortium
(Pisa)
- 18.15 - 18.30 | Creatinine and CK plasma concentrations: possible role as biomarkers and correlation with age and muscular function in BMD.**
P. Riguzzi, V. Zangaro, M. Villa, M. Cestarollo, E. Pegoraro, L. Bello (Padova)
- 18.30 - 18.45 | Titin truncating variants and their downstream effect on TTN transcripts**
M. Savarese, M. Jobari, A. Vihola, H. Luque, TTN-RNAseq Working Group, P. Hackman, B. Udd (Folkhalsan Research Center)

Friday, 3rd December 2021

- 08.00 - 08.40 | Early Symposium:**
Myotubular Myopathy (MTM)
Chairman: Angela Berardinelli
 • MTM and natural history of the disease | *Adele D'Amico*
 • Atypical clinical aspects of MTM | *Cristina Molera*

- 08.40 - 10.00 | Workshop 4 - Update on mitochondrial disease**
Chairman: *Michelangelo Mancuso*
 • New emerging phenotypes | *Guido Primiano*
 • Biomarkers and outcome measures in mitochondrial disease: from diagnosis to clinical trials | *Costanza Lamperti*
 • Multi-omics approaches to improve mitochondrial disease diagnosis | *Dario Ronchi*
 • New therapeutic approaches: Small Molecules | *Michelangelo Mancuso*
- 10.00 - 10.30 | Invited Lecture**
Latest developments in Facioscapulohumeral Dystrophy
Introduction: *Rossella Tupler*
Guest: *Nicol Voermans*
- 10.30 - 11.30 | Workshop 5**
Inflammatory myopathies
Chairman: *Giovanni Antonini*
 • Histopathological diagnosis | *Matteo Garibaldi*
 • Immune-mediated Necrotizing Myopathy | *Daniele Velardo*
 • Innovative treatments | *Massimiliano Mirabella*
- 11.30 - 12.00 | Invited Lecture “Recent update on dermatomyositis”**
Introduction: *Carlo Minetti*
Guest: *Ichizo Nishino*
- 12.00 - 13.00 | Symposium**
Patient assessment in view of new treatments for Pompe disease
Chairmen: *Antonio Toscano*
 • Glycogen storage disease | *Tiziana Mongini*
 • Pre-symptomatic patients | *Olimpia Musumeci*
 • Respiratory disorders | *Grazia Crescimanno*
- 14.00 - 15.30 | ORAL COMMUNICATIONS 3**
Myopathies and muscular dystrophies: new phenomic, genomic, and pathogenetic aspects
Chairmen: *Grazia D'Angelo, Paola Tonin*
- 14.00 - 14.15 | Genotype-related respiratory progression in Duchenne Muscular Dystrophy – multicentre international study**
F. Trucco, D. Ridout, K. Maresb, M. Chesshyre, P. Munot, A. Sarkozy, S. Robb, R. Quinlivan, M. Riley, C. Wallis, E. Chan., F. Abel, S. De Lucia, J.-Y. Hogrel, E. H. Niks, I. de Groot, L. Servais, V. Straub, V. Ricotti, A. Manzur, F. Muntoni (London, UK; Paris, France; Leiden, The Netherlands; Liège, Belgium; Oxford, UK; Newcastle Upon Tyne, UK)

- 14.15 - 14.30 | Five years next-generation sequencing approach to neuromuscular symptoms and the prevalence of COL VI variants**
G. Marinella, B. Buchignani, A. Rubegni, G. Astrea, D. Cassandrini, MA Donati, M. Filosto, S. Gallone, F. Giannini, D. Lopercolo, MA Maioli, F. Magri, A. Malandrini, P. Mandich, F. Mari, R. Massa, S. Matà, M. Moggio, TE Mongini, E. Pegoraro, F. Ricci, G. Ricci, C. Rodolico, G. Siciliano, M. Sperti, C. Ticci, P. Tonin, FM Santorelli, R. Battini (Pisa; Firenze; Brescia; Torino; Siena; Cagliari; Milano; Genova; Roma; Padova; Messina; Verona)
- 14.30 - 14.45 | Improved use of the CPMS platform through tailored online training: the Italian EURO-NMD experience**
F. Bianchi, F. Fortunato, F. Giannini, A. Malandrini, V. Silan, N. Ticozzi, S. Fenu, S. Bonanno, C. Peduto, P. D'Ambrosio, G. Primiano, C. Sancricca, M. Sciacco, R. Brusa, M. Filosto, S. Cotti Piccinelli, E. Pegoraro, L. Solero, G. Gadaleta, C. Brusa, M. Cateruccia, D. Diodado, A. Pugliese, G. Nicocia, A. Ferlini, G. Siciliano (Pisa; Ferrara; Siena; Milano; Napoli; Roma; Brescia; Padova; Torino; Messina)
- 14.45 - 15.00 | Unveiling the relation between autophagy and Pompe disease**
F. M. Monasta, F. Blasevich, R. Mantegazza, L. Maggi, C. Bragato (Milano)
- 15.00 - 15.15 | Is fat detrimental for bone health in DMD? Insights from a longitudinal study.**
C. Panicucci, N. Brolatti, M. Pedemonte, E. Casalini, C. Minetti, M. Maghnie, C. Bruno, N. Di Iorgi (Genova)
- 15.15 - 15.30 | Preliminary Genome-Wide Association Study for identification and characterization of genetic modifiers of Duchenne muscular dystrophy**
D. Sabbatini, S. Vianello, A. Fusto, B. Merlo, A. Berardinelli, S. Parravicini, C. Bruno, C. Panicucci, G. P. Comi, F. Magri, A. D'Amico, M. Catteruccia, L. Travaglioni, Grazia D'Angelo, V. Sansone, A. Di Bari, T. Mongini, C. Brusa, L. Maggi, E. Canioni, A. Gallone, M. Pane, D. Leone, L. Politano, E. Picillo, V. Nigro, S. Messina, G. Vita, G. Sorarù, L. Bello, E. Pegoraro (Padova; Genova; Milano; Roma; Bosisio Parini (Lecco; Torino; Napoli; Messina)
- 15.30 - 17.15 | ORAL COMMUNICATIONS 4**
Natural history and new diagnostic tools in neuromuscular disorders
 Chairman: *Giorgio Tasca, Sabrina Ravaglia*
- 15.30 - 15.45 | Limb girdle muscular dystrophy type R1/2A and R2/2B: three decades of natural history**
A. LoMauro, E. Diella, A. Russo, M. Delle Fave, C. Pistininzi, E. Marchi, R. Pascuzzo, S. Vantini, A. Aliverti, M.G. D'Angelo (Milano)
- 15.45 - 16.00 | Comorbidities in Myasthenia Gravis: a report from 178 patients**
S. Iacono, V. Di Stefano, A. Lupica, A. Gagliardo, P. Lanza, M.G. Rispoli, L. Ferri, F. Brighina, A. Di Muzio (Palermo; Chieti)

- 16.00 - 16.15 | **A clinical follow up study in a cohort of Italian children affected by LMNA gene mutations.**
B. Buchignani, G. Marinella, A. Rubegni, D. Cassandrini, S. Frosini, F.M. Santorelli, G. Astrea, R. Battini (Pisa)
- 16.15 - 16.30 | **Congenital myasthenic syndrome: natural history of an Italian cohort of patients**
A. Gallone, A. Pugliese, S. Bonanno, M. Garibaldi, C. Rodolico, L. Maggi (Milano; Messina; Roma)
- 16.30 - 16.45 | **Refractory Myasthenia Gravis: characteristics of an Italian cohort of patients**
G. Nicocia, A. Pugliese, R. Frangiamore, S. Bonanno, A. Gallone, C. Antozzi, F. Baggi, C. Rodolico, R. Mantegazza, L. Maggi (Milano; Messina)
- 16.45 - 17.00 | **Linked-read WGS as further step to study unsolved NMD cases**
M.E. Onore, A. Torella, F. Musacchia, F. Del Vecchio Blanco, P. D'Ambrosio, M. Zanolio, G. Piluso, V. Nigro (Napoli; Pozzuoli)
- 17.00 - 17.15 | **Immunofluorescence signal intensity measurements as a semi-quantitative tool to assess sarcoglycan complex expression in muscle biopsy**
F. Poggetti, F. Magri, M. Ripolone, M. Sciacco, M. Moggio, G.P. Comi, S. Zanolio (Milano)
- 17.15 - 18.45 | **ORAL COMMUNICATIONS 5**
Myopathies and muscular dystrophies: new phenotypes, biomarkers, and therapies – 2
Chairmen: Giovanni Meola, Monica Sciacco
- 17.15 - 17.30 | **Medaka fish as a new model to investigate skeletal muscle performance**
M. Marcello, I. Morotti, M. Caremani, M. Savarese, B. Udd, I. Conte, V. Nigro, M. Linari (Firenze; Helsinki, Finland; Pozzuoli; Napoli)
- 17.30 - 17.45 | **Characterization of DNA methylation status of the D4Z4 locus as epigenetic biomarker for the molecular diagnosis of FSHD**
V. Caputo, D. Megalizzi, C. Bax, M. Ranieri, L. Colantoni, G. Tasca, E. Ricci, C. Caltagirone, R. Casella, E. Giardina, C. Strafella (Roma)
- 17.45 - 18.00 | **AIGkit, the mobile app for patients with Pompe disease: results and future perspectives**
E. Lai, G. Ricci, E. Schirinzi, G. Siciliano (Pisa)
- 18.00 - 18.15 | **Selective P2X7 antagonism ameliorates the dystrophic phenotype of a-sarcoglycan-deficient mice by dampening muscle inflammation and fibrosis**
L. Raffaghello, E. Principi, S. Baratto, C. Panicucci, S. Pintus, F. Antonini, G. Del Zotto, S. Bruzzone, P. Scudieri, C. Minetti, E. Gazzero, C. Bruno (Genova; Berlin, Germany)

- 18.15 - 18.30 | **Antisense oligonucleotide (ASO)-based in vitro modulation of GAA expression in Late-Onset Pompe Disease**
D. Ronchi, S. Lucchiari, F. Magri, M. Garbellini, S. Salani, S. Zanotti, P. Ciscato, M. Sciacco, M. Moggio, S. Corti, N. Bresolin, GP Comi (Milano)
- 18.30 - 18.45 | **Solve unsolved neuromuscular cases: collaborative reanalysis of WES data through the Solve-RD Genome-Phenome Analysis Platform (GPAP).**
A. Torella, R. Zeuli, A. Varavallo, F. Del Vecchio Blanco, C. Angelini, N. Brunetti Pierri, A. Wischmeijer, Solve-RD DITF-EuroNMD, G. Piluso, V. Nigro (Napoli; Telethon Institute of Genetics and Medicine (TIGEM); Padova; Bolzano)
- 18.45 | **Assemblea Soci AIM**

Saturday, 4th December 2021

- 08.30 - 09.30 | **Wake up Muscle Club**
 Chairmen: *Chiara Fiorillo, Giulia Ricci*
- 08.30 - 08.42 | **"Sudden weakness in a 56-year-old Asian male"**
B. Labella, D. Pezzini, A. Costa, L. Poli, M. Magoni, A. Padovani (Brescia)
- 08.42 - 08.54 | **"A case of severe sensorimotor polyneuropathy and distal myopathy associated with vocal cord and pharyngeal weakness"**
A. Manini, D. Velardo, P. Ciscato, C. Cinnante, F. Magri, M. Moggio, GP Comi, S. Corti, D. Ronchi (Milano)
- 08.54 - 09.06 | **"Reorientation of muscle biopsy as a diagnostic hint"**
M. Meznaric, J. Zidar (Ljubljana, Slovenia)
- 09.06 - 09.18 | **"A case of exercise intolerance and deafness"**
C. Panicucci, M. Traverso, A. Pini, M. Giannotta, M.L. Valentino, M. Scala, M. Pedemonte, C. Minetti, F. Zara, C. Fiorillo, C. Bruno (Genova; Bologna)
- 09.18 - 09.30 | **"Cognitive impairment and slowly progressive muscular weakness in a 6-year-old boy"**
S. Antognozzi, F. Magri, P. Ciscato, L. Napoli, D. Velardo, G. Scuvera, A. Giacobbe, D. Milani, M. Sciacco, M. Moggio, S. Corti, N. Bresolin, GP Comi, D. Ronchi (Milano)
- 09.30 - 11.00 | **Workshop 6**
Next generation molecular diagnostics
 Chairmen: *Vincenzo Nigro, Filippo Santorelli*
 • EXPEDITing in vivo gene therapy with AAV vectors | *Alberto Auricchio*

- How to integrate genomic and exomic data in clinical practice | *Alessandra Ferlini*
- The risk of false positives and false negatives in genomic data; The SOLVE RD experience | *Steven Laurie*
- Genetic approach to undiagnosed myopathies | *Vincenzo Nigro*

11.00 - 12.30 | AIM meets Patients and Family Associations

Chairmen: *Carlo Minetti, Gabriele Siciliano, Luisa Politano*

- UILDM 60 years of activity - *Marco Rasconi*
- Telethon Registries - *Anna Ambrosini*
- Voice to the Associations (*AIDMED, AIG, AMAR, AISED, Altro Domani, ASAMSI, Ass Dodò, AICa3, COL6, Di.MIO, Famiglie SMA, FMM,FSHD It, GFB, Mitocon, Parent Project, UILDM, and others*)

12.30 | Awards Ceremony for the best works

13.00 | Conclusions

**XXI Congresso
Nazionale**

Associazione Italiana di Miologia

**POSTER
SESSION**

Poster Session

Thursday, 2nd December 2021

15.15 - 17.00 | POSTER – CHANNEL 1

Dystrophinopathies and muscular dystrophies

Chairmen: *Luca Bello, Adele D'Amico*

15.15 - 15.23 | Care for adults with Duchenne Muscular Dystrophy (DMD): a single centre experience.

C. Brusa, E. Rolle, F. Rossi, I. Cavallina, R. D'Alessandro, G. Gadaleta, G. Urbano, F. Ricci, T. Mongini (Torino)

15.23 - 15.31 | Becker Muscular Dystrophy and 7q11.23 microduplication syndrome in a boy with developmental delay, bicuspid aorta and interatrial septum defect

E. Picillo, P. D'Ambrosio, L. Passamano, A. Torella, V. Nigro (Napoli; Messina; Pozzuoli)

15.31 - 15.39 | Cerebral alteration patterns in children with Duchenne Muscular Dystrophy: a machine learning approach on magnetic resonance images

D. Peruzzo, T. Ciceri, S. Mascheretti, V. Lampis, F. Arrigoni, A. Giubergia, F. M. Villa, A. Crippa, M. Nobile, E. Mani, A. Russo, M. G. D'Angelo (Bosisio Parini)

15.39 - 15.47 | Detection of dystrophin isoforms transcripts in human adult control brain using in-situ RNA analysis

M.S. Falzarano, M. Mietto, R. Rossi, F. Fortunato, R. Selvatici, M. Gessi, F. Montanaro, J. Morgan, F. Muntoni, A. Ferlini (Ferrara; London, UK; Roma)

15.47 - 15.55 | A novel DMD gene splice-site variant in an Italian boy with Becker muscular dystrophy: a clinical and genetic study

G. Lanzi, B. Risi, S. Cotti Piccinelli, A. Galvagni, C. Romani, C. Fiorillo, M. Traverso, C. Bruno, A. Padovani, M. Filosto (Brescia; Genova)

15.55 - 16.03 | Delay in Duchenne Muscular Dystrophy Progression with Eteplirsen: Longer Time to Loss of Ambulation Versus Standard of Care

J. Iff, G. Bungey, A. Paine, B. Han, H. Gordish-Dressman, E. Henricson, L. Picaro, C. McDonald (Cambridge, Massachusetts, USA; London, UK; Washington DC, USA; California, USA)

16.03 - 16.11 | Disease characterization of ambulant patients with Becker muscular dystrophy: histopathological, functional and imaging data from Givinostat trial cohort

D. Velardo, M. Ripolone, S. Zanotti, F. Magri, C. M. Cinnante, S. Montrasio, S. Cazzaniga, E. H. Niks, M. Sciacco, P. U. Bettica, G. P. Comi (Milano; Leiden, the Netherlands)

16.11 - 16.19 | Evaluation of 6MWT as functional measure in Becker muscular dystrophy

V. Zangaro, L. Bello, P. Riguzzi, M. Villa, S. Mastellaro, M. Cestarollo, E. Pegoraro (Padova)

16.19 - 16.27 | An integrative splicing predictor pipeline to prioritise DMD deep intronic variants

R. Zeuli, M. Zanobio, M.E. Onore, F. Romano, M.M. Napoli, E. Picillo, A. Torella, F. Del Vecchio Blanco, G. Piluso, V. Nigro (Napoli; Pozzuoli)

16.27 - 16.35 | [Antisense morpholino-based in vitro correction of a novel pseudoexon-generating mutation in the SGCB gene](#)

F. Magri, S. Salani, F. Fortunato, S. Zanotti, P. Ciscato, S. Gerevini, L. Maggi, M. Sciacco, M. Moggio, S. Corti, N. Bresolin, D. Ronchi, GP Comi
(Milano; Bergamo)

16.35 - 16.43 | [Two cases of autosomal dominant Ullrich congenital muscular dystrophy due the same de novo mutation in the COL6A3 gene](#)

E. Picillo, L. Passamano, A. Torella, F. Del Vecchio Blanco, M.E. Onore, M. Zanolio, R. Zeuli, L. Politano, A. Selicorni, V. Nigro (Napoli; Pozzuoli; Como)

16.43 - 16.51 | [Oculo-pharyngeal muscular dystrophy: phenotypic and genotypic studies in Abruzzo](#)

M.G. Rispoli, L. Ferri, P. Ajdinaj, A. Di Muzio (Chieti-Pescara; Chieti)

15.15 - 17.00 | POSTER - CHANNEL 2

Myasthenia, inflammatory myopathies, channelopathies

Chairmen: Carmelo Rodolico, Matteo Garibaldi

15.15 - 15.23 | [Characterization of p.N1180I sodium channel mutant associated to myotonia and myopathy in Italian patients](#)

C. Altamura, A. Farinato, C. Campanale, M. R. Carratù, J.-F. Desaphy (Bari)

15.23 - 15.31 | [Mutations associated with hypokalemic periodic paralysis: from hotspot regions to complete analysis of CACNA1S and SCN4A genes.](#)

R. Brugnoli, E. Canioni, M. Filosto, A. Pini, P. Tonin, T. Rossi, C. Canavese, M. Eoli, G. Siciliano, G. Lauria, R. Mantegazza, L. Maggi
(Milano; Brescia; Verona; Ancona; Torino; Pisa)

15.31 - 15.39 | [SARS-CoV-2 infection in myasthenic patients from Liguria](#)

E. Scarsi, S. Grisanti, A. Cella, E. Narciso, C. Cabona, A. Beronio, A. Assini, M. Del Sette, F. Bandini, L. Benedetti, V. Prada, A. Schenone, M. Grandis (Genova; La Spezia; Iowa City, IA, USA)

15.39 - 15.47 | [COVID-19 vaccine and dermatomyositis: is there an association?](#)

P. Ajdinaj, L. Ferri, M. G. Rispoli, F. Barbone, M. A. De Rosa, D. Angelucci, G. Andreassi, M. Amatetti, P. Amerio, A. Di Muzio (Chieti-Pescara; Ortona)

15.47 - 15.55 | [A very late onset AChR and MuSK double positive myasthenia gravis](#)

A. Pugliese, P. D'Ambrosio, G. Nicocia, S. Messina, A. Toscano, C. Rodolico (Messina)

15.55 - 16.03 | [Congenital myasthenia associated with new variant of the PREPL gene](#)

M. Traverso, M. Scala, S. Baratto, M. Di Duca, C. Campana, M. Cataldi, C. Panicucci, M. Pedemonte, C. Bruno, C. Minetti, F. Zara, C. Fiorillo (Genova)

16.03 - 16.11 | [Rituximab in Refractory Myasthenia Gravis: what we learned after 10 years. A single centre experience.](#)

G. Greco, E. Frezza, M. Goglia, L. Boffa, R. Massa (Roma)

16.11 - 16.19 | Impact of COVID-19 and vaccines in myasthenia gravis: experience from an Italian cohort

A. Lupica, V. Di Stefano, S. Iacono, A. Pignolo, M. Quartana, A. Gagliardo, B. Fierro, F. Brighina (Palermo)

16.19 - 16.27 | Mutation of LRSAM1 gene: a novel cause of congenital myasthenic syndrome.

A. Pugliese, G. Nicocia, P. D'Ambrosio, S.A. Musumeci, A. Toscano, C. Rodolico (Messina; Troina)

15.15 - 17.00 | POSTER – CHANNEL 3

Myopathies

Chairmen: Enzo Ricci, Lorenzo Maggi

15.15 - 15.23 | Severe progressive course in an NLSDM patient put on MCT dietary treatment

C. Angelini, S. Missaglia, D. Tavian (Padova; Milano)

15.23 - 15.31 | The role of muscle biopsy: A 15 years single center experience.

S. Cotti Piccinelli, E. Baldelli, B. Risi, F. Caria, A. Padovani, M. Filosto (Brescia; Fano)

15.31 - 15.39 | Respiratory function in Myotonic Dystrophy Type 1: a Retrospective Study

C. R. Ferrari Aggradi, E. Falcier, A. Lizio, A. Pirola, J. Casiraghi, A. Zanolini, E. Carraro, L. Mauro, F. Rao, E. Roma, A. Iannello, E. De Mattia, A. Barp, S. Lupone, V. Gatti, C. Italiano, V. A Sansone (Milano)

15.39 - 15.47 | Establishing Biomarkers and Clinical Endpoints in Myotonic Dystrophy Type 1 (END-DM1): Italian experience

M.C. Frisoni, C. Ferrari-Aggradi, L. Mauro, A. Di Bari, J. Refran, S. Becchiati, F. Iossa, A. Zanolini, K. Eichinger, J. Dekdebrun, J. St Romain, N. Johnson, C. Thornton, VA Sansone (Milano; Rochester, New York; Richmond, VA)

15.47 - 15.55 | Cardiac magnetic resonance findings and outcome in type 1 myotonic dystrophy

M. Leali, A. Aimo, G. Ricci, G. Todiere, G. Vergaro, C. Grigoratos, A. Giannoni, F. Torri, F. Baldinotti, G. Donato Aquaro, G. Siciliano, M. Emdin, C. Passino, A. Barison (Pisa)

15.55 - 16.03 | A novel distal vacuolar myopathy caused by a large expansion of the PLIN4 gene- clinical, histological and imaging data.

L. Maggi, S. Gibertini, E. Iannibelli, A. Gallone, C. Bragato, S. Bonanno, F. Blasevich, R. Mantegazza, M. Mora, A. Ruggieri (Milano)

16.03 - 16.11 | Prevalent muscle involvement in two siblings with Glycogen Storage Disease type III

L. Passamano, M. Savarese, A. Torella, M. Scutifero, E. Picillo, A. Palladino, V. Nigro, L. Politano (Napoli; Helsinki, Finland; Pozzuoli)

16.11 - 16.19 | "Natural history of skeletal muscle laminopathies: a 2-year prospective study"

L.S. Santovito, S. Bonanno, B. Pasanisi, A. Gallone, F. Ricci, I. Tramacere, R. Zanin, S.C. Previtali, L. Maggi (Chicago, IL, USA; Milano; Torino)

16.19 - 16.27 | Muscle MRI images in patients with Chronic Progressive External Ophthalmoplegia

M. Sperti, C. Nesti, M. Bartolini, F.M. Santorelli, S. Matà (Firenze; Pisa)

16.27 - 16.35 | Psychopathology and coping styles in patients with neuromuscular disorders: a follow-up study during the COVID pandemic

M. Nobile, A. Tarabelloni, F. Tizzoni, P. Colombo, A. Tesei, A. Russo, M. Molteni, S. Previtali, Y. Falzone, A. Berardinelli, M.G. D'Angelo (Bosisio Parini; Milano; Pavia)

16.35 - 16.43 | Late-onset diffuse myalgias and multiple subarachnoid cysts. A case report

F. Torri, L. Chico, F. Baladinotti, M.A. Caligo, M.R. D'Apice, G. Ricci, G. Siciliano (Pisa)

15.15 - 17.00 | POSTER – CHANNEL 4

SMA and motor neuron disorders

Chairmen: Antonio Di Muzio, Tiziana Mongini

15.15 - 15.23 | Dysregulation of lncRNAs and mRNA targets during skeletal muscle development in a patient-derived induced pluripotent stem cell (iPSC) model of Amyotrophic Lateral Sclerosis.

E. Giagnorio, C. Malacarne, E. Salvi, P. Bossolasco, D. Bardelli, A. Ratti, G. Lauria, R. Mantegazza, S. Bonanno, S. Marcuzzo (Milano; Monza)

15.23 - 15.31 | Insights for the development of a miRNA-based therapeutic strategy in ALS exploiting iPSC-derived motor neurons and exosomes.

V. Melzi, M. Rizzuti, D. Gagliardi, M. Meneri, P. Masrori, F. Biella, P. Van Damme, GP Comi, M. Nizzardo, S. Corti (Milano; Leuven, Belgium)

15.31 - 15.39 | Quantitative MRI evaluation of muscle involvement of lower limbs in amyotrophic lateral sclerosis (ALS): a pilot longitudinal study

M. Paoletti, L. Diamanti, S.I. Muzic, E. Ballante, F. Solazzo, L. Foppoli, X. Deligianni, S. Santini, S. Figini, N. Bergsland, A. Picchiechio (Pavia; Basel, CH; Buffalo, NY, United States; Milano)

15.39 - 15.47 | Parental mosaicism in AARS1 – related hereditary neuropathy

M. Neri, E. Sette, F. Fortunato, C. TrabANELLI, A. Margutti, P. Rimessi, M. Fabris, V. Tugnoli, F. Gualandi, R. Selvatici, A. Ferlini (Ferrara)

15.47 - 15.55 | Use of 3d printer in a rehab lab for the creation of customized assistive devices with users with radiation-induced brachial plexopathy to increase participation: case study

F. Pilla, P.G. Ianes, S. Casagrande, B. Gasperini, R. Zuccarino (Trento)

15.55 - 16.03 | Quality of life assessment in adult spinal muscular atrophy patients treated with nusinersen

S. Bonanno, R. Zanin, L. Bello, I. Tramacere, V. Bozzoni, L. Caumo, M. Ferraro, S. Bortolani, G. Sorarù, M. Silvestrini, V. Vacchiano, M. Turri, R. Tanel, R. Liguori, M. Coccia, R. E. Mantegazza, T. Mongini, E. Pegoraro, L. Maggi (Milano; Padova; Torino; Ancona; Bologna; Bolzano; Trento)

16.03 - 16.11 | Exploring face mobility in SMA

E. Carraro, E. Pegolo, F. Cibir, MC Frisoni, F. Salmin, S. Becchiati, Z. Sawacha, VA Sansone (Milano; Padova)

16.11 - 16.19 | 6MWT as measure of fatigability in sma type 3 patients treated with nusinersen

A. Govoni, G. Ricci, M. Meneri, S. Bonanno, L. Bello, C. Caponnetto, L. Passamano, M. Grandis, F. Trojsi, F. Cerri, G. Gadaleta, V. Bozzoni, L. Caumo, R. Tanel, E. Saccani, V. Vacchiano, G. Sorarù, E. D'Errico, I. Tramacere, S. Bortolani, G. Pavesi, R. Zanin, M. Silvestrini, L. Politano, A. Schenone, S.C. Previtali, A. Berardinelli, M. Turri, L. Verriello, M. Coccia, R. Mantegazza, R. Liguori, M. Filosto, M. Maioli, G. Marrosu, I.L. Simone, T. Mongini, S. Corti, E. Pegoraro, G. Siciliano, G. Comi, L. Maggi (Milano; Pisa; Genova; Napoli; Torino; Parma; Bologna; Bari; Ancona; Pavia; Bolzano; Udine; Brescia; Cagliari)

16.19 - 16.27 | Neurofilament light chain and Profilin-1 in adult SMA patients under nusinersen treatment: 26-months follow up

G. Musso, V. Bozzoni, L. Caumo, L. Bello, C. Cosma, G. Sorarù, M. Plebani, E. Pegoraro (Padova)

16.27 - 16.35 | Cell-penetrating peptides-conjugated Morpholino: a novel therapeutic approach for the treatment of Spinal Muscular Atrophy symptomatic cases

M. Rizzuti, M. Bersani, E. Pagliari, M. Garbellini, D. Saccomanno, N. Bresolin, G. P. Comi, S. Corti, M. Nizzardo (Milano)

16.35 - 16.43 | Oro-facial and bulbar involvement in SMA (OBI-SMA): outcome measures & end-point assessments

F. Salmin, C. Cattaneo, J. Lops, E. Carraro, G. Coratti, MC Pera, A. Pirola, A. Di Bari, E. Albamonte, A. Zanolini, G. Palazzo, L. Mauro, M. Pane, E. Mercuri, VA Sansone (Milano; Roma)

16.43 - 16.51 | The experience with Nusinersen (Spinraza) in pediatric SMA patients in Emilia-Romagna in a regional network

G. Scarpini, M. Giannotta, R. Not, P. Capelli, C. Testoni, F. Pisani, B. Piccolo, C. Fusco, D. Frattini, G. Vergine, M. Farina, J. Sarajlia, F. Marchetti, G. Piccinini, A. Pini (Bologna; Parma; Reggio Emilia; Rimini; Romagna; Ravenna)

ABSTRACTS OF ORAL COMMUNICATIONS

(in alphabetical order of the first Author)

Session 1

Clinical and demographic features of patients with SMA on treatment with risdiplam: the iSMAC experience

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Background. Risdiplam has been approved for Compassionate Use (CUP) since 2019, for SMA type 1 and type 2 who could not receive the approved treatment for the disease. It's an orally administered drug targeting SMN2 gene. More than 200 patients have had access to this program in Italy, up to June 2021.

Aims. To describe the clinical and demographic features of patients included in CUP amongst the iSMAC Italian centers.

Methods. This is a retrospective study including demographic, neuromotor, respiratory and nutritional data, shifts, adverse events and dropouts.

Results. 44 out of 576 Italian iSMAC patients (7.6%) are on risdiplam (8 SMA1, 36 SMA2). Age ranges: 0-10 yrs (n = 1, SMA2); 11-17 yrs (n = 13, 4 SMA1, 9 SMA2); 18-25 yrs (n = 15, 3 SMA1, 12 SMA2); 18-25 yrs (n = 15.3 SMA1, 12 SMA2) and older than 25 yrs (n=14 SMA2). The majority (73%) are non-sitters. Concerning respiratory status, 6 patients are in invasive-ventilation, 26 use NIV and 8 patients do not require respiratory support. Regarding the nutritional status, 11 have a PEG and 12 have dysphagia. About 20% of patients switched from nusinersen for difficulties in intrathecal administration. 3 dropped-out respectively for side-effects, subjective inefficacy, shift to gene therapy.

Conclusions. Considering the criteria to access risdiplam so far, all but one are older than 11 yrs, have se-

vere motor, nutritional and respiratory conditions and are naive due to inaccessibility to nusinersen for technical difficulties. After open clinical use, further follow-up data will provide information on additional reasons and number of patients accessing risdiplam.

Amifampridine safety and efficacy in ambulatory SMA type 3 patients: a randomized, placebo-controlled, crossover, phase 2 trial

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Spinal muscular atrophy (SMA) is an autosomal recessive disease where a deficient amount of SMN protein leads to progressive degeneration of bulbar and spinal motor neurons. Therapies for the restoration of SMN production are now available. Yet, fatigue and signs of impaired neuromuscular junction (NMJ) transmission have been documented as possible contributors to SMA phenotype.

Amifampridine (3,4-diaminopyridine, AP), a voltage-dependent K⁺ channel blocker, prolongs depolarization of the presynaptic NMJ terminal, enhancing neuromuscular transmission.

Here, we evaluated the safety and efficacy of AP in ambulatory patients with SMA type 3, in a 1:1 randomized, double-blind, placebo-controlled, 2-period, 2-treatment, crossover study.

Type 3 SMA, able to walk unaided for 30m, entered the run-in phase during which AP was titrated up to an optimized stable dose. Then, patients with at least 3-points improvement in Hammersmith Functional Motor Score Extended (HFMSE) were randomized to receive either AP or placebo for 2 weeks, alternatively, for a total of 28 days of double-blind treatment. Efficacy was evaluated by changes from randomization of HFMSE, quality of life, 6-minute walk test. Descriptive analyses and a mixed effects linear model were used for statistic.

Six patients for each sequence of treatment were randomized. Transient paresthesias (33,3%) were the only

AP-related AEs reported. AP treatment led to a statistically significant improvement in HFMSE (LS Mean Difference 0.792 (0.22 to 1.37), $p = 0.0083$), compared to placebo, but not in the secondary endpoints.

SMA-001 study provided evidence that AP was safe and effective in treating ambulatory patients affected by SMA type 3.

IND/EUDRACT number: 106263 /2017-004600-22

FIREFISH Part 2: 24-month efficacy and safety of risdiplam in infants with type 1 spinal muscular atrophy (SMA)

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Objective. To determine the efficacy and safety of risdiplam in infants with type 1 spinal muscular atrophy (SMA) after 24 months of treatment.

Background. SMA is a severe, progressive neuromuscular disease caused by reduced levels of survival of motor neuron (SMN) protein due to deletions and/or mutations of the *SMN1* gene. A second *SMN* gene, *SMN2*, produces only low levels of functional SMN protein.

Risdiplam (EVRYSDI™) is a centrally and peripherally distributed oral SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein.

Design/methods. FIREFISH (NCT02913482) is a multicenter, open-label, two-part study of risdiplam in infants with type 1 SMA and two SMN2 gene copies, aged 1-7 months at enrollment. Part 1 ($n = 21$) assesses the safety, tolerability and pharmacokinetics/pharmacodynamics of different risdiplam doses. Part 2 ($n = 41$) assesses the efficacy and safety of the Part 1-selected dose.

Results: The primary endpoint of Part 2 at 12 months was met (data-cut: 14th November 2019); 29% ($p < 0.0001$, performance criterion = 5%) of infants were able to sit without support for ≥ 5 seconds, as measured by the Bayley Scales of Infant and Toddler Development, Third Edition. This milestone was never achieved in natural history cohorts. No treatment-related safety findings leading to withdrawal were reported in Part 2. Efficacy and safety data from infants in Part 2 who have received risdiplam treatment for 24 months will be presented.

Conclusions. Part 2 is ongoing and will provide important data on the long-term efficacy and safety of risdiplam in infants with Type 1 SMA.

Long-term nusinersen safety and effects on motor function in adult spinal muscular atrophy type 2 and 3

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Objective. To retrospectively investigate long-term safety and efficacy of nusinersen in a large cohort of adult Italian SMA patients.

Methods. Inclusion criteria were: 1) clinical and molecular diagnosis of SMA2 or SMA3; 2) nusinersen treatment started in adult age (> 18 years); 3) clinical data available at least at baseline (beginning of treatment) and 14 months.

Results. We included 112 patients (15 SMA2 and 97 SMA3) with median age at first administration of 35 years (range 18-74). Median period of treatment was 30 months (range 14-38). The Hammersmith Functional Rating Scale Expanded (HFMSSE) in SMA3 patients increased significantly from baseline to the end of the follow-up ($p = 0.0013$), with higher improvement in walkers (median +2, $p = 0.0147$) than in sitters (median 0, $p = 0.0384$). The Revised Upper Limb Module (RULM) in SMA3 significantly improved between baseline and the end of the follow-up ($p = 0.0002$), with higher effect in sitters (median +2, $p = 0.0024$) than in walkers (median 0, $p = 0.0281$). Conversely, SMA2 patients had no significant changes of median HFMSSE and RULM over the observational period. Furthermore, six-minute walking test distance significantly increased in SMA3 walkers during the follow-up (mean +35 m, $p = 0.0003$). Conclu-

sions: Our data provide the first evidence of prolonged nusinersen safety and efficacy in a large cohort of adult SMA2 and SMA3.

Onasemnogene abeparvovec palliative care experiences and challenges in type 1 spinal muscular atrophy: the oldest care for the newest drug?

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Type 1 spinal muscular atrophy (SMA1) is the most severe and common form of SMA. Its poor life expectancy has been drastically improved after the advent of gene therapy.

In our centre, we have recently treated four patients with Onasemnogene abeparvovec (Zolgensma).

Two were novel diagnoses (one female, one male), the other two were already being treated with antisense oligonucleotides (males). The median age of diagnosis was 5.5 months; the median age of treatment was 25 months.

Gene therapy was administered by a neurologist and the pediatric palliative care (PPC) team specialists provided the following interventions: 1) communication of diagnosis, helping the parents to choose the treatment for their baby in line with their values and beliefs; 2) training the parents to administer respiratory, nutritional and physical therapies 3) training the family paediatrician, the home care nurses, and local hospital personnel 4) performing regular visits at home to monitor the patients and further train the parents 5) guaranteeing psychological and social support.

Families' main issues were daily managing the long-term disease burden and accepting a possible variability in the therapy outcome.

From the medical perspective, communication with families, verifying their global comprehension, and mediating their expectations and attitudes (especially when switching from oligonucleotides), was additionally demanding.

Neurological follow-up with periodic assessments is currently ongoing.

To conclude, in the growing panorama of innovative SMA therapies, PPC supportive approaches based on continuous multidisciplinary and comprehensive clinical, rehabilitative, and social strategies maintain an essential role.

Session 2

Myalgia and fatigue as long term symptoms in COVID-19 patients: a 1-year follow-up

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Background. COVID-19 is caused by SARS-CoV-2 virus and in many cases lead to a pneumonia. However a number of neuromuscular manifestations have been associated to SARS-CoV-2 infection. Furthermore, multiorgan symptoms after COVID-19 are being reported by increasing numbers of patients, ranging from cough to fatigue and muscle pain. However, the long-term health consequences of COVID-19 remain largely unclear.

Methods: We evaluated 124 patients hospitalized between march and May 2020 for SARS-COV-2 associated pneumonia at 6 and 12 months. We retrospectively collected clinical, laboratory and radiological information available. for each patient, cognitive tests, scales for depression and anxiety and a specific Fatigue Severity Scale (FSS) were performed.

Results. Twenty-five patients died during hospitalization. At 12 months follow up 85 patient were evaluated.

Eighty-seven (70%) patients were male and mean age was 67.3 years.

During hospitalization 43 (36.5%) of patients complain of myalgia. This patients had higher CK levels than patients who did not (534 U/L vs 93 U/L, $p < 0.001$).

At 12 months 42% of patients complain about myalgia while 34% about fatigue. Mean FSS value were 32.93, and were significantly higher in patients who complain about fatigue (41.52 vs 27.08 $p < 0.001$) and Muscle pain (40.84 vs 26.80, $p < 0.001$) compared to who did not.

Conclusions. During hospitalization for COVID-19 myalgia was associated with an higher level of CK, suggesting a possible muscle involvement. At 12 month myalgia and fatigue were present in a more than a third of patient suggesting that this manifestation could be one of the main COVID-19 sequelae.

Phenotypic spectrum of IGHMBP2 gene mutations and natural history study in a cohort of European patients

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Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a rare childhood autosomal recessive motor neuron disease, due to recessively inherited *IGHMBP2* gene mutations. The main hallmarks of the disease are diaphragmatic palsy and progressive distal muscular atrophy and paralysis. In few cases mutations in the same gene led to Charcot-Marie Tooth disease type 2S (CMT2S). There is no treatment and very little data are available on the disease progression. We present the data of a European patients' cohort composed of 15 patients with SMARD1, aged between 5 months and 21 years and 2 patients with CMT2S respectively 16 and 63 years old. Clinical data have been collected retrospectively and prospectively. For SMARD1 patients the disease onset was before 5 months, manifesting with weak crying, feeding difficulties, hypotonia, club foot and acute respiratory distress. All patients need continuous ventilatory support (12 via tracheostomy while 3 with NIV) and G-tube was necessary in 12 cases. Head control was reached only by 60% of the patients, independent sitting only by 27%. Autonomic dysfunction and scoliosis were observed in all patients. The two CMT2S patients manifested with distal motor neuropathy respectively at 8 and 10 years, both of them are still ambulant. Diseases related

to IGHMBP2 mutations are very rare and with heterogeneous clinical manifestations. Our case studies broaden the knowledge relating to the phenotype and natural course of these disorders, providing useful data for the evaluation of possible future therapeutic strategies.

ASPIRO gene therapy trial in X-Linked Myotubular Myopathy (XLMTM): update on preliminary efficacy and safety findings

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We present updated results from ASPIRO (NCT03199469), investigating gene replacement therapy with AT132 for XLMTM patients. XLMTM, an ultra-rare, life-threatening myopathy caused by mutations in the *MTM1* gene, leads to impaired neuromuscular and respiratory function, and early death. Patients enrolled required ventilator support and had no clinically significant underlying liver disease at baseline, defined as > 5x ULN ALT or AST, or hepatic peliosis by imaging. As of July 2020, efficacy data were analysed for 16 patients (n = 6, 1 x 10¹⁴ vg/kg (age 0.8-4.1 years at dosing); n = 10, 3 x 10¹⁴ vg/kg (age 1.3-6.8 years at dosing). At baseline, all patients required ventilator support (mean [SD] 22.4 [3.34] hours/day), and missed critical motor milestones. Treated patients had significant reductions in daily hours of ventilator dependence vs control (p < 0.0001 for both doses); seven achieved ventilator independence. Treated patients showed significant improvements in motor function vs control, and acquired and maintained several major motor milestones. Muscle biopsies demonstrated durable myotubularin expression with improved pathology scores at 48 weeks. Three patients treated at 3x10¹⁴ vg/kg, experienced fatal sepsis or gastrointestinal bleeding with ongoing severe cholestatic liver dysfunction. As of September 2021, the ASPIRO program is placed on a clinical hold by the FDA following the death of a newly dosed participant at 1 x 10¹⁴ vg/kg; the cause of death is still pending. Present understanding is that these events

are related to a combination of gene therapy and underlying XLMTM disease process. Safety of AT132 is being closely monitored as the four patient deaths are being thoroughly investigated.

Safety, Beta-sarcoglycan expression, and functional outcomes from systemic gene transfer of rAAVrh74.MHCK7.hSGCB in LGMD2E/R4

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Objective. Limb-girdle muscular dystrophy type 2E/R4 (LGMD2E/R4) is caused by mutations in the beta-sarcoglycan gene (*SGCB*), resulting in loss of SGCB protein and other components of the dystrophin-associated protein complex (DAPC). LGMD 2E/R4 manifests as progressive hip/shoulder muscle weakness. This first-in-human, phase 1/2 trial (NCT03652259) evaluated SRP-9003, a self-complementary rAAVrh74.MHCK7.hSGCB construct restoring SGCB.

Methods. Patients aged 4-15 years with SGCB mutation (both alleles) received 1 SRP-9003 IV infusion: Cohort 1 (n = 3), 1.85 x 10¹³ vg/kg; Cohort 2 (n = 3), 7.41 x 10¹³ vg/kg. Endpoints included safety (primary), SGCB expression (secondary), and function (North Star Assessment for Limb-girdle Type Muscular Dystrophies [NSAD], time to rise [TTR], 4-stair climb [4-sc], 100-meter timed test [100 m], 10-meter timed test [10 m]).

Results. We report Year 2 (Y2; Cohort 1) and Year 1 (Y1; Cohort 2) results. As of January 2021, SRP-9003 was well tolerated with no new safety signals since the previous data cut (July 2020); adverse events occurred early and were manageable. Immunofluorescence showed robust SGCB expression post treatment, leading to DAPC reconstitution, maintained to Y2 (Cohort 1). SRP-9003-treated patients showed functional improvements, maintained at Y2 in Cohort 1 (NSAD, +5.7 points; TTR, -0.6 s; 4-sc, -0.3 s; 100 m, -2.8 s; 10 m, -0.2 s) and Y1 in Cohort 2 (NSAD, +4 points; TTR, -1.1 s; 4-sc, -0.4 s; 100 m, -7.9 s; 10 m, -0.6 s). Post hoc analysis showed improved NSAD outcomes versus untreated natural history cohort (9.2-point difference, Y2; 95% CI, 3.2-15.1).

Conclusions. Results suggest long-term efficacy of SRP-9003, supporting advancement of the clinical development program.

Study Support. Sarepta Therapeutics, Inc.

Disclosures. LRR-K, ERP, SL, DAG, ASM, EK, SN, XL, and LP are or have been employees of Sarepta Therapeutics, Inc, and may own stock in the company. LNA and LPL received fees from Sarepta Therapeutics, Inc, for licensure of the LGMD natural history data set. JRM received financial support from Sarepta Therapeutics, Inc, for travel to meetings to present any products sponsored by Sarepta. KJL, KC, NFR, MAI, and BP have no conflicts to disclose. Product is investigational only.

An integrated and multiparametric system to identify diagnostic and prognostic parameters in neuromuscular diseases towards trials readiness

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We are working on an integrated, multiparametric approach in diagnosis and management of neuromuscular diseases (NMDs) by using a single support software platform, potentially useful in implementing diagnosis and taking care towards trials readiness. Promising preliminary results have been obtained to date with the Health360 platform under the umbrella of the InGene 2.0 project. Health360, a platform developed under the Software-as-a-Service (SaaS) principles, merges all that, with sections dedicated to the collection of personal data (under the premises of the EU 2016/679 GDPR Regulation), as well as modules devoted to biomedical images storage and interpretation. In particular, further modules, including neurological examination and functional motor tests, muscular MRI, genetic data, muscle biopsies, are under development and optimization. The possibility to upload such images in a common, user-friendly software platform, where data and image storage, as well as the analysis of images and loops can be performed in an intelligent manner, would be of extreme aid to the clinician. If confirmed on larger cohorts and with robust statistical approach, such results could drive the present tool to be used for diagnostic aims, phenotypic characterization and clinical follow-up.

Creatinine and CK plasma concentrations: possible role as biomarkers and correlation with age and muscular function in BMD

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Objectives. To collect creatinine and CK plasma concentration in a cohort of BMD patients, in order to explore their role as biomarkers and correlation with age and muscular function.

Materials and methods. We collected 110 CK values in a cohort of BMD patients whose muscular function was assessed by NSAA score; for 27 patients (26.5%) we had more than one value. We also collected 61 serum creatinine values.

We correlated CK (log10 transformed) and creatinine values with age and muscular function of patients.

Results. The mean value of CK levels in our cohort was 2090 U/L (\pm SD 3596 U/L), while the median was 903 U/L. We expected a decrease in CK values during years; in fact, the negative association between CK values and age was strongly significant ($r = -0.63$, $p < 0.0001$). CK decrease was loosely correlated with the reduction of NSAA score ($r = 0.19$, $p = 0.043$). The mean value of creatinine levels in our cohort was 0.59 mg/dL (\pm SD 0.27 mg/dL), while the median was 0.49 mg/dL. The relationship between creatinine and muscular function was statistically significant, with normal creatinine values in patients with preserved muscular function, and low creatinine values in patients with deteriorated muscular function ($r = 0.61$, $p < 0.0001$). Creatinine tended to decrease with age, but in our cohort this association was not statically significant ($r = 0.2$, $p = 0.115$).

Discussion and conclusions. Creatine and CK plasma concentrations seem to correlate well with muscle mass and function in BMD, as observed also in other neuromuscular diseases. Future perspectives include the evaluation of potential changes of these biomarkers with novel therapeutic interventions.

Titin truncating variants and their downstream effect on TTN transcripts

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Titin truncating variants (TTNtv) have been associated with a dominant cardiomyopathy showing a reduced, age dependent, penetrance but they also cause recessive

skeletal muscle diseases. The mechanisms explaining the TTNtv role in dominant cardiomyopathies and in recessive skeletal muscle titinopathies are still unclear.

We analysed by RNA sequencing 44 skeletal muscle samples from patients with a confirmed or a suspected titinopathy, proving variants causing a premature stop codon out of the M-band to result in a nonsense mediated decay (NMD) of titin transcripts. Vice versa, stop codons in the M-band escape NMD and still result in a 'quasi-full-length' protein.

Although most TTNtv cause splicing defects, their effect on the transcripts is highly variable. Most of the splice variants we have characterized cause in-frame losses or gains, still resulting in a near-full length protein. Moreover, some of them affect only a reduced number of transcripts and a significant amount of normal protein is still produced.

A direct analysis of RNA, cDNA and protein is crucial to characterize the effect of truncating variants. These second-tier studies are mandatory to support the variant classification of DNA changes and to clarify the pathomechanisms of rare diseases.

Session 3

Improved use of the CPMS platform through tailored online training: the Italian EURO-NMD experience

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Background. In order to ease diagnosis and treatment of rare diseases afflicting 30 million people in Europe, the EU had created the European Reference Networks (ERNs), connecting cross-border healthcare providers. Among the ERN features is the Clinical Patients Management System (CPMS), a digital web-based software where clinicians can discuss about patients through virtual panels, sharing patients' data securely. The CPMS requires careful training for its correct use, hence a twelve-month project funded by Sarepta Therapeutics was set up to improve the use of the CPMS among Euro-NMD ERN Italian members.

Methods. In the first two months, two medical doctors (MD) underwent a teaching course with a CPMS expert. Afterwards, the two MDs organized and managed a training course across four months with a flexible schedule to ease the course attendance. In a further phase lasting five months, the trainers focused on panels' progression so to ease the moving forward across the panel timeline and ease panel closure by attendees. Several new panels were opened.

Results. At the end of the course, participants had opened 98 panels (approximately 80% of the total in the whole Euro-NMD ERN). The participants managed to access the platform and became acquainted in using it, and the course strengthened the Italian network overall.

Conclusions. Cross-border virtual consulting is an outstanding tool to improve the quality of health care provision. Our results show that a training course tailored to healthcare professionals might boost the usability of the CPMS, increasing its impact to European health system.

Unveiling the relation between autophagy and Pompe disease

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Perturbation of glycolytic enzymes results in glycogen storage disorders such as Pompe disease (PD), which is an autosomal recessive metabolic pathology due to a defect of the lysosomal enzyme acid α -glucosidase (GAA), necessary for glycogen degradation. PD was the

first glycogen storage disorder linked to autophagy, a key molecular mechanism that maintains cellular homeostasis and ensures correct macromolecule turnover in the cell.

Despite the significant results achieved in this disease comprehension, it remains unclear how autophagy is disrupted in PD, since it is yet unknown if an excessive acceleration or reduction of this process is present.

The importance of understanding autophagy dysfunction relies in the fact that this could explain the difficulties of current therapies in restoring muscle function, in particular in late onset patients. Moreover, could explain the presence of secondary symptoms in PD patients, in particular related to neuromuscular junction (NMJ) malfunctioning.

Taking advantage of the zebrafish transgenic line Tg(CMV:EGFP-map1Lc3b), characterized by fluorescent autophagosomes, we generated a new zebrafish PD model, useful for the deep study of autophagic pathway. Exploiting different drugs known to have effects on autophagy, we are investigating this pathway at immunohistochemistry, biochemistry, electron microscopy and behavioral level.

We believe that our findings will trigger a reassessment of the PD pathogenic mechanisms, as well as the research of new therapeutic targets addressing both glycogen accumulation and autophagy. Furthermore, this investigation will be essential to explore if the secondary symptoms of PD could be reversible.

Five years next-generation sequencing approach to neuromuscular symptoms and the prevalence of COL VI variants

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Objective. In this study we applied next generation sequencing (NGS) in undiagnosed patients with suspected neuromuscular disease to investigate the prevalence of variants in collagen VI and collected clinical and instrumental data to verify the real pathogenicity of these variants.

Methods. As part of InGene project, we screened 241 neuromuscular genes of which COL6A1, COL6A2, COL6A3 by NGS in 580 patients with neuromuscular disorders referred to Molecular Medicine Lab of IRCCS FSM in the last five years. Variants in collagen VI were classified according to reference literature and were collected independently by clinical picture. Clinical data available were collected in a CRF and missing data were updated with referred clinician.

Results. We identified "probable" or "likely pathogenic" disease-related mutations in *COLVI-related* genes in 47 patients (26 male and 21 female). 11 patients harboured variants in *COL6A1* gene, 18 patients had a variant in *COL6A2* gene, 21 patients had a variant in *COL6A3* gene. Collected clinical and instrumental data partially reflect the phenotype described in literature.

Conclusions. This study shows both the prevalence of collagen VI variants in patients with weak muscular symptoms and highlights the advantages of NGS used as a first level diagnostic approach especially for complex genes that are difficult to study routinely. Anyhow, it also demonstrates the difficulty of considering these variants as pathogenetic without clinical and instrumental data. It may therefore be useful to outline a flow chart to verify the real pathogenicity of found variants.

Is fat detrimental for bone health in DMD? Insights from a longitudinal study

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We evaluated bone mass acquisition and fragility fractures determinants in 26 ambulant prepubertal DMD patients treated with deflazacort. DXA measurements of total body less head (TB-BMD Z-score), lumbar spine bone mineral density (LS-BMD Z-score) and body fat (TBF%) were obtained at baseline (T0) and every year up

to 3 years (T3). A delta-TBZ-score/year [(T3_TB-BMD Z-score - T0_TB-BMD Z-score)/years] was used for a better interpretation of bone changes. On day of DXA, subjects underwent anthropometric measurements and dosage of serum bone turnover biomarkers.

Median age was 7.7 years (IQR 6/9,2) at T0 and 11.4 years (IQR 9.8/13.4) at T3. At T3, the incidence of fractures was 23.1%, at a median age 12.3 years (IQR 10.7/14.3).

Between T0 and T4 we observed a decline of HtSD ($p = 0.001$) and TB-BMD Z-score ($p = 0.004$), an increase in TBF% ($p = 0.04$), while BMI SD, LS-BMD Z-score and serum biomarkers did not change significantly. Multiple regression analysis identified TBF% as the only negative predictor of TB-BMD Z-score, and higher BMI SD at T0 was associated to greater negative delta-TBZ-score/year ($r = -0.63$; $p < 0.001$).

Compared to fracture-free-DMD, fractured-DMD showed 2 times greater delta-TBZ-score/year ($p < 0.05$) and 2,3 times increased TBF%/year ($p < 0.05$). Fractures were predicted independently by delta-TBZ-score/year, BMI SDS and TBF% at T3.

In conclusion, we demonstrated for the first time a detrimental effect of the fat tissue on bone fragility, and we showed that TB-BMD Z-score represents a reliable tool to detect bone changes in ambulant DMD, suggesting its inclusion in trials assessing the efficacy of bone treatments in DMD.

Preliminary Genome-Wide Association Study for identification and characterization of genetic modifiers of Duchenne muscular dystrophy

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Background. One of the most challenging hurdles that clinical researchers face in the Duchenne muscular dystrophy (DMD) field is the considerable inter-patient variability in age at presentation and weakness progression: that is, the relevant phenotypic variability of DMD. Increasingly, it is recognized that the genetic background, i.e. genetic variation in genes different from disease gene, may modulate Mendelian disease phenotype. These trans-acting variants are called genetic modifiers. Several modifiers of DMD have been identified through candidate gene studies, while genome-wide association studies have only been initially attempted.

Aim. This work represents a preliminary analysis of a genome-wide association study (GWAS) looking for DMD modifier loci, that plans to collect clinical data and DNA samples from ~700 DMD patients followed by Consortium of Italian Centers, that in the last decade have collaborated to studies of DMD natural history.

Materials. The GWAS was carried out using the high-density Illumina Infinium Omni2.5Exome-8 genotyping chip, version 1.5, and implemented a pipeline for data interpretation based on ad-hoc scripts. The association test was a regression test of age at loss of ambulation, with the following covariates: glucocorticoid treatment (at least 1 year while ambulatory) and DMD mutation type.

Results. So far, we genotyped about 50% of the planned total cohort. The algorithm identified an association signal with a p value of 4.2×10^{-8} in an intronic region at chromosome 6q22.1, whose functional meaning needs to be further elucidated.

Conclusions. Identified SNPs represent putative modifiers of the phenotype of DMD. We plan to validate these findings by expanding sample size, and validating top association signals in independent cohorts.

Genotype-related respiratory progression in Duchenne Muscular Dystrophy – multicentre international study

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Introduction and aims. Mutations amenable to skipping of specific exons have been associated with different motor progression in Duchenne muscular dystrophy (DMD). Less is known about their association with long-term respiratory function.

We aimed to investigate the features of respiratory progression in four DMD genotypes relevant for ongoing exon skipping therapeutic strategies.

Methods. This was a retrospective longitudinal study including DMD children followed by the UK North Star network and international AFM network centres (May 2003-October 2020). We included boys amenable to skip exons 44, 45, 51 or 53, older than 5 years and ambulant at first recorded visit. Subjects who were corticosteroid-naïve or enrolled in interventional clinical trials were excluded. The progression of respiratory function (absolute forced vital capacity, FVC, and calculated as percentage of predicted, FVC%) was compared across the four subgroups (skip44, skip45, skip51, skip53).

Results. We included 142 boys. Mean (SD) age at first visit was 8.6 (2.5) years. Median follow-up was 3(0.3-8.3) years. In skip45 and skip51 FVC% declined linearly from first recorded visit. From the age of 9 years FVC% linearly declined in all genotypes. Skip44 had the slowest (2.7%/year) and skip51 the fastest (5.9%/year) annual FVC% decline. The absolute FVC progressively increased in skip44, skip45, skip51. In skip53 FVC started declining from 14 years of age.

Discussion. The progression of respiratory dysfunction follows different patterns for specific genotype categories. This information is valuable for prognosis and for the evaluation of exon skipping therapies.

Session 4

A clinical follow up study in a cohort of Italian children affected by LMNA gene mutations

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Objective. To assess the clinical course and genotype-phenotype correlations in patients with neuromuscular disorders due to LMNA/C gene mutations.

Methods. We analysed clinical and genetic data in a cohort of Italian paediatric patients with a neuromuscular disorder and a pathogenetic or likely pathogenetic mutation in LMNA/C. Clinical data included motor function, scoliosis, respiratory and heart function, laboratory and imaging data.

Results. Nine patients aged 1-20 years were included in our retrospective study. The mean age at onset was 23 ± 25 months, ranging from birth to 6 years. The patients in the cohort ranged from those with congenital muscular dystrophy (CMD) to patients with myopathic features. All the patients with myopathic features remained independently ambulant and presented a mild phenotype. None of the patients developed conduction system defects or arrhythmia but merely minor heart problems (mild tricuspid insufficiency).

In our CMD patients, mutations were mainly present in the first part of the coding region (IF domain), and the two patients, whose mutations were in exon 1, presented the worst phenotype. One of them lost ambulation at the age of 2 while the other never acquired it; both needed nocturnal non-invasive ventilation.

Conclusions. Our findings are consistent with literature, showing an evident correlation between the severity of the muscle phenotype and the protein domain affected. Half of our paediatric patients had a CMD phenotype while the others presented myopathic features highlighting, yet again, that a mutation in LMNA/C in paediatric aged patients may be associated with mild phenotypes.

Limb girdle muscular dystrophy type R1/2A and R2/2B: three decades of natural history

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Introduction. Defining the natural history of a disease is an essential requisite to any therapeutic intervention. Slow progression, different pathogenic mechanisms and small number of patients have been the most relevant factors interfering with definition of markers of disease progression in LGMD2A and 2B.

Patients and methods. Patients with LGMDR1/LGMD2A and LGMDR2/LGMD2B attending the IRCCS “E. Medea” in the last 30 years were recruited. Demographic data, muscular strength in at least 14 muscles (Medical Research Council grading); motor function (Motor Function Measures scale, 6 min walk test and Performance of Upper Limb scale); cardiopulmonary function and swallowing capability data were collected. A previously developed regression model was used to reconstruct the evolution over time of each measurements.

Results. 428 visits of nineteen 2A and twenty 2B patients were retrospectively analysed through the regression model to create the curves of evolution with disease duration of muscle strength, motor and cardio-pulmonary function tests. Relevant muscular and motor function alterations occurred after the first decade of disease, while mild respiratory function alterations started after the second, with preserved cardiac function. Although type 2A showed relatively stronger distal lower limb muscles, while type 2B started with relatively stronger upper limb muscles, the corresponding motor functions were similar, becoming severely compromised after 25 years of disease.

Conclusions. This was the longest retrospective study in types 2A and 2B. It defined muscular, motor, cardiac and respiratory function curves of disease evolution that could be used to evaluate how the natural progression is changed by therapies.

Congenital myasthenic syndrome: natural history of an Italian cohort of patients

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Background. Congenital myasthenic syndromes (CMS) are genetic diseases characterized by impairment of neuromuscular junction structure or function. CMS

natural history has been poorly investigated and has not been clarified yet. Aim of this study is to longitudinally assess the disease progression of CMS in an Italian cohort of patients.

Methods. We included patients with a clinical and molecular diagnosis of CMS, followed in three Italian neuromuscular centres. Patients were evaluated at baseline and then once per year, with a minimum follow-up of 1 year. Neurological examination included the Myasthenia Gravis-specific Activities of Daily Living scale (MG-ADL) and the MG-composite scale (MGC).

Results. A total of 33 patients, including 13 males and 20 females, were enrolled. The most common mutated gene was CHRNE (n = 13 pts), followed by DOK7 (n = 4 pts) and COLQ (n = 3 pts). Mean age at first evaluation was 41.8 ± 14.4 years (range = 10-71) and mean follow-up period was 2.1 ± 0.4 years (range = 1-3). Mean MG-ADL and MGC scores at baseline were 5.9 ± 4.0 and 14.9 ± 8.2 , respectively. At the end of follow-up period, a mean reduction of 1 point for MG-ADL and 2.9 points for MGC were found, with improvement usually related to treatment modifications. MG-ADL did not change between first and last evaluation in around half of the patients (n = 19), while MGC resulted stable in 11 (33.3%) patients.

Conclusions. Our preliminary data suggest a disease stability according to MG-ADL and MGC in most of the CMS patients over the follow-up period.

Comorbidities in Myasthenia Gravis: a report from 178 patients

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Background and aims. Myasthenia Gravis (MG) is an autoimmune disorder with fluctuating weakness of the skeletal muscles causing significant disability and morbidity. The development of specialized care centers for MG patients as well as the employment of new effective treatments improved the survival in MG. The most common MG therapies may worsen preexisting patients’ comorbidities or they may be contraindicated in such situation. We explored the frequency of comorbidities in MG compared to healthy controls (HCs) and how they are distributed in MG according to age at disease onset, gender, and disease severity.

Materials and methods. Patients with MG attending to Neuromuscular Clinic of University Hospital “Paolo Giaccone” of Palermo and “SS Annunziata” Hospital

of Chieti were enrolled to study whereas HCs living in Sicily and Abruzzo were collected using a web-available questionnaire. The Chi-squared test was used to compare qualitative variables and the distribution of comorbidities between groups with level of significance set to $p < 0.05$.

Results. N = 178 patients with MG (mean age 59 years, 55% male) and 178 sex- and age matched healthy controls were enrolled. The 87% of MG patients and the 76% of HCs from comorbidities ($p = 0.006$). Comorbidities in MG were differently distributed according to age at disease onset and gender. In patients with MGFA class III-IV-V respiratory disorders ($p = 0.009$) and thymoma ($p = 0.003$) were more common.

Conclusions. MG patients showed higher prevalence of comorbidities than HCs. Assessing of MG comorbidities may allow the clinicians to optimize the MG management.

Refractory Myasthenia Gravis: characteristics of an Italian cohort of patients

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Background. Refractory myasthenia gravis (MG) has been poorly investigated to date.

Aim. To describe the clinical features of drug-refractory patients with MG in a large Italian cohort.

Methods. We included 756 ocular and generalized MG patients from 2 Italian Neuromuscular Centers, with MG onset between 2000 and 2018 and at least one year of follow-up. Patients were classified as refractory when remained unchanged or worsened, according to MG Foundation of America post-Interventional Status (MGFA-PIS), with persistent symptoms or drug-related side effects, after treatment with steroids and at 2 least steroid-sparing immunosuppressive agents, administered in adequate doses for an appropriate period, as established by literature.

Results. Mean disease duration of the whole cohort patients was 11.2 ± 5.16 years (range 1-44). Fifty-nine (7.8%) patients were identified as refractory. The mean age at onset of refractory MG was 44 ± 17.2 years (range 16-83), slightly lower than in non-refractory subgroup, although not significant. Females were predominant in both refractory and non-refractory MG patients, but females were significantly more frequent among the former subgroup (67.8%, $p < 0.0001$). Similarly, thymoma was more frequently observed in the refractory MG patients (18/59; p-value: 0.002). Conversely, antibodies to MuSK

(7/59) were not significantly associated to refractory MG. Recurrent need of rescue therapy as intravenous immunoglobulin or plasma exchange, were significantly more frequently observed in the refractory subgroup (p-value: 0.029).

Conclusions. Our study emphasises that the drug-refractory patients represent a small but considerable MG subgroup with specific features, needing an adequate management and new emerging treatment options.

Linked-read WGS as further step to study unsolved NMD cases

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Although gene panels, WES or WGS analysis have changed our approach to molecular diagnosis, many genetic conditions remain unsolved. To define the large rearrangements in the DMD gene which are the most common cause of dystrophinopathies including Duchenne (DMD) and Becker (BMD) muscular dystrophy, we have applied the linked-read sequencing technology developed by 10x Genomics. The distinction between alleles along the genome through phasing is the main advantage of 10x linked-read technology. As an exemplary case, we studied a DMD carrier with an unsolved genetic status, linked to a 6-year-old boy affected by an X-linked muscular dystrophy. Despite a deletion of exons 16-29 in *DMD* gene was responsible for BMD phenotype in male of her family, MLPA and array-CGH analysis in the carrier showed a normal dosage of these exons and an increased dosage of flanking exons 1-15 and 30-34. The linked-read WGS was able to phase both X chromosomes, showing two different rearrangements: a deletion of exons 16-29 on one allele and a de novo duplication of exons 1-34 on the other one in the *DMD* gene. By data analysis, this duplication not only restores the normal dosage of exons 16-29 but involves a region of 1.52 Mb spanning the *DMD* gene and the 5' upstream region. In conclusion, our results demonstrate that linked-read WGS can be a useful tool for improving our understanding of unsolved genetic conditions in a very feasible way.

Immunofluorescence signal intensity measurements as a semi-quantitative tool to assess sarcoglycan complex expression in muscle biopsy

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Sarcoglycanopathies diagnosis is genetically determined but muscle analysis, by immunohistochemistry and western blot, is still mandatory for a correct diagnostic process. In sarcoglycanopathies, clinical severity is usually correlated with the quantity of residual protein even if a deficiency in a single component of the sarcoglycan protein complex generally leads to concomitant reduction or loss of other sarcoglycans. There is no current therapy for sarcoglycanopathies, one of the most innovative therapeutic approaches is based on the use of adenoviral vectors for restoring protein expression, so the availability of a method that allow objective quantification of the membrane protein, faster than western blot, could be useful in evaluating the efficacy of pharmacological treatment. Moreover immunofluorescence provides the opportunity to a simultaneous evaluation of protein quantity and sarcolemma positioning, not achievable by western blot.

Muscle biopsies of 13 patients affected with genetically defined sarcoglycanopathy (8 LGMD-R3, 3 LGMD-R4 and 2 LGMD-R5), were analysed histologically and for immunofluorescence and western blot expression of each of the sarcoglycans. Laminin-2, was used as sarcolemmal reference for membrane integrity and as internal standard of fluorescent reaction. Quantification of integrated density of fluorescent signal was performed using ImageJ software. Further analysis of immunofluorescence and western blot data obtained from these patients by Bland-Altman plot, to evaluate the level of agreement of two methods, suggested that the difference was acceptable.

Preliminary results show that this semi-quantitative tool could contribute to better define patient's prognosis and could be useful to evaluate the efficacy of potential pharmacological treatments during clinical trials.

Session 5

Characterization of DNA methylation status of the D4Z4 locus as epigenetic biomarker for the molecular diagnosis of FSHD

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Introduction. The diagnosis of FacioScapuloHumeral Dystrophy (FSHD) is complicated the high clinical variability and incomplete penetrance. Therefore, the availability of reliable (epi)genetic biomarkers is desirable for providing patients with more accurate molecular diagnoses and genotype-phenotype correlations.

Aim of the study. The study aimed at assessing the methylation status of the D4Z4 locus with the purpose of enhancing the molecular diagnosis of FSHD.

Materials and methods. The study involved 307 subjects (137 with clinical diagnosis of FSHD, 20 with LGMD and 150 controls). DNA methylation levels of the DR1 region (1kb upstream of the DUX4-ORF within the D4Z4 array), the DUX4-PAS (the distal part of the array) and its CpG6 site were assessed on genomic DNA by means of Bisulfite Sequencing and Capillary Electrophoresis.

Results. FSHD subjects showed significantly ($p < 0.01$) hypomethylation levels (0.30 ± 0.09 , 0.49 ± 0.13 and 0.69 ± 0.18) compared to LGMD and controls subjects (0.38 ± 0.05 , 0.60 ± 0.07 and 0.88 ± 0.06) for DR1, DUX4-PAS and CpG6, respectively. Interestingly, patients carrying pathogenic mutations in FSHD-associated genes displayed lower DR1 methylation (0.15 ± 0.08 vs 0.31 ± 0.05) compared to wild-type patients. These results suggested that the methylation profile of the D4Z4 represents a useful biomarker for discriminating FSHD subjects from controls or patients with other myopathies.

Conclusion. The present study showed that the analysis of the methylation levels of D4Z4 region could support the molecular diagnosis of FSHD, by enhancing the genotype-phenotype correlation; orienting the specialist towards a deeper genomic analysis addressed to detect pathogenic variants in causative/modifier genes or perform differential diagnosis (LGMD, other myopathies).

AIGkit, the mobile app for patients with Pompe disease: results and future prospectives

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AIGkit is an easy-to-use mobile application, created with the aim of allowing a telematic interaction between

adult patient with Pompe disease and clinicians that can be downloaded for free on smartphone. After a first phase, whose results were presented as oral communication at AIM congress in 2018 and 2019, and published as original article in *Neuromuscular Disorders*, the second operational phase of the project has been activated for its use in real life and clinical practice. The pre-established goal has been therefore to create an informatic platform for the collection of clinical data where each patient can access through the personal app on their smartphone, in order to allow the registration of their data and facilitate interaction with their clinicians. The design activity and procedures, despite the difficulties encountered in the various phases also caused by the Sars-COVID-19 emergency, were carried out to meet the requirements of the privacy guarantor, in order to activate the use of the platform and the real-time sharing of the data collected remotely on the app of each patients. We are now planning the dissemination of the initiative at national level and the implementation of this project in collaboration with other clinical centers that will be able to use the servers of the Azienda Ospedaliera Universitaria Pisana (AOUP) as coordinating center, thus improving value and utility for users, both patients and clinicians.

Medaka fish as a new model to investigate skeletal muscle performance

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Teleosts are commonly used in biomedical research to investigate the molecular mechanisms underlying human diseases. The medaka fish (*Oryzias latipes*) is a well-established vertebrate model used in developmental biology and genetic studies involving fast genetic manipulation, real-time images of developing pathologies and drug efficacy tests. We explored the possibility to use it to determine the performance of intact skeletal muscle at sarcomere level. Optically transparent tails of nine days-old medaka fish larvae were mounted in a thermoregulated trough containing physiological solution between the lever arms of a strain gauge force transducer and a loudspeaker motor at a sarcomere length (SL0) of $2.0 \pm 0.1 \mu\text{m}$. Tetanic contractions were elicited by trains of stimuli (200Hz for fused tetanus) at 10°C. A striation follower (Huxley et al. *J Physiol* 1981;317:12-13P) was used to record sarcomere length changes during contraction in a 0.8 - 1.0 mm long segment selected along the central region of the sample. The force-

velocity (T-V) relation was determined in afterloaded contractions and the power output at each load was calculated as the product between the imposed load and the steady shortening velocity. In fixed end conditions the plateau tetanic force ($62 \pm 8 \text{ kPa}$, mean \pm SEM, $n = 3$) was attained with a half-sarcomere shortening against the end compliances of about 8% SL0. The unloaded shortening velocity, determined by fitting Hill equation to the T-V data, and the maximum power output are $5.9 \pm 0.3 \text{ L0/s}$ and 70 mW/g , respectively. These preliminary results make the medaka fish a promising model to investigate the genotype/phenotype correlation in skeletal muscle diseases. Supported by the EJP-RD.

Selective P2X7 antagonism ameliorates the dystrophic phenotype of a-sarcoglycan-deficient mice by dampening muscle inflammation and fibrosis

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Alpha-sarcoglycan (SGC) deficient muscular dystrophy, also called Limb Girdle muscular disease R3, is an inherited disorder resulting from mutations in the a-sarcoglycan gene and aggravated by chronic inflammation that is finely modulated by the extracellular (e) ATP/purinoreceptors axis. Genetic ablation of P2X7 and pharmacological inhibition of the eATP-P2X7 axis by the broad-spectrum antagonist oxidized-ATP alleviated dystrophic phenotypes and dampened the local inflammatory response in mice affected by Duchenne muscular dystrophy and α -sarcoglycanopathy.

Aim of this study is to evaluate the therapeutic effectiveness and to characterize the underlying mechanism of A438079, a potent and selective P2X7 antagonist, in a-sarcoglycan-deficient mice (Sgca mice).

Our results show that treatment of Sgca mice with A438079 ameliorated the dystrophic phenotype without any detectable side effects. Recovery was evident in the key functional and biochemical parameters such as improved muscle performance and decreased serum creatine kinase levels. The benefits of A438079 treatment were also reflected by the muscle morphology where

we observed a drastic reduction of the extent of local fibrosis and inflammation. A detailed characterization of muscle inflammatory infiltrates indicated that A438079 significantly decreased the percentage of neutrophils, activated monocytes, macrophages and dendritic cells in comparison to untreated dystrophic mice (Sgca control). In contrast, immunosuppressive regulatory T cells were significantly increased in Sgca A438079-treated mice in comparison to Sgca control animals.

In conclusion, the pharmacological inhibition of P2X7 by the selective antagonist A438079 might provide a safe therapeutic approach to ameliorate the dystrophic phenotype in a-sarcoglycanopathy by decreasing local fibrosis, inflammation and muscle degeneration.

Antisense oligonucleotide (ASO)-based in vitro modulation of GAA expression in late-onset Pompe disease

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Pompe disease is a lysosomal storage disorder caused by acid alpha-1,4-glucosidase deficiency due to GAA mutations. Late-onset form (LOPD) displays progressive muscle weakness with respiratory involvement often leading to premature death. ERT is the only approved therapy, but this treatment is expensive and requires life-long biweekly infusion. Some patients are non-responders, and the appearance of autoantibodies lead to therapy suspension. Additional therapies must be investigated. Antisense oligonucleotides (ASO) have been previously used to rescue the GAA leaky splicing mutation IVS1-32-13T > G (resulting in exon 2 skipping), the most frequent molecular defect found in LOPD patients worldwide.

We administered modified ASO (MOE1 and MOE2, 50 nM) targeting a GAA transcriptional repressor (MOE1) and a regulator element promoting exon 2 skipping (MOE2) into fibroblasts of 4 LOPD patients. Three days after delivery both MOE1 and MOE2 increased GAA transcript levels (from +60% to +140% versus untreated), accompanied by the restoration of physiological exon 2 splicing by MOE2 (from +49% to +180% versus untreated). The efficacy of the molecular approach was validated by biochemical and immunocytochemical methods. We did observe a significant increase of GAA stability (up to 30% of control cells) and activity as well as a reduction of intracellular glycogen content. MOE2

provided superior results compared to MOE1. The effect was maintained up to 6 days after transfection. Our findings confirm and expands previous data on the efficacy of antisense strategy aiming to increase GAA activity and support the development of ASO-based therapeutic approaches in LOPD.

Solve unsolved neuromuscular cases: collaborative reanalysis of WES data through the Solve-RD Genome-Phenome Analysis Platform (GPAP)

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Solve-RD is a Horizon 2020-supported project that aims to solve a large number of unsolved rare diseases. As part of the European Reference Network for Neuromuscular Disease (ERN-EURO-NMD), we have contributed to this effort by sharing WES data from a large cohort of unsolved neuromuscular patients and their affected and unaffected relatives. The fastq files from 362 individuals (204 males and 157 females), corresponding to 223 families, were uploaded into the Genome-Phenome Analysis Platform (<https://platform.rd-connect.eu/>) together with a comprehensive HPO-based description of the phenotype, and processed using the RD-Connect bioinformatics pipeline. Using automated data filtering for SNV-Indels variants, the reanalysis identified the causative variant in three previously unsolved cases. A missense mutation in CASQ1 (Asp244Gly) caused asymmetrical limb myopathy in a family with autosomal dominant inheritance. A de novo mutation occurred in the other two families: the first with a missense mutation in ACTA1 (Pro334Ser) that caused a congenital myopathy, the second one with a missense mutation in SYT1 (Ile368Thr) in a pediatric patient affected by severe developmental delay and hypotonia. To date, about 1.3% of our shared cases have been solved, in line with the performance obtained from the other ERNs, which altogether account for about 3% of solved cases. Additionally, shared data from all Solve-RD participants can be searched for genes, variants, and phenotypes sub-groups, helping in further investigations, as well as the definition of novel genotype-phenotype correlations and identifying new genes involved in neuromuscular disorders.

MUSCLE CLUB SESSION

(in alphabetical order of the first Author)

Thyrototoxic hypokalemic periodic paralysis as a rare differential diagnosis: a case report

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Thyrototoxic hypokalemic periodic paralysis (THPP) is an uncommon emergency mainly affecting Asian men. The classic triad for diagnosis is: paralysis, thyrotoxicosis and hypokalemia. The typical presentation consists of symmetrical proximal muscle weakness (with legs more affected than arms, with extensor muscle more involved than flexors). We present the case of a 56-years-old Asian male who was hospitalized because of sudden onset of weakness and pain of lower limbs. He reported six months history of palpitations and hands tremors. Neurological examination showed mild symmetrical paraparesis, hyporeflexia, hands tremors, no sensory or cranial nerve deficits. He had fever (body temperature 37.4°C), profuse sweating and atrial fibrillation. Magnetic resonance imaging of spine and nerve conduction studies were normal. Laboratory data revealed potassium 2.7 mmol/L (3.4-4.5), thyroid stimulating hormone < 0.005 mIU/L (0.270-4.200), thyroxine 65.3 ng/L (9.3-17.0), and triiodothyronine 16.0 ng/L (2.0-4.4), TSH receptor antibody 11.1 IU/L (< 1.8) and anti thyroperoxidase > 600.0 kIU/L (< 34.0). He was treated with potassium supplementation, Propranolol, Methimazole and Propylthiouracil with prompt improvement of symptoms. TPP is the most common form of acquired periodic paralysis, yet diagnosis may be challenging in case of new-onset thyroid disorder. Hypokaliemia linked due to hyperactivity of NaK-ATPase stimulated by thyroid hormones is the key of pathophysiology of TPP. Diagnosis is based on clinical and biochemical elements. Management of THPP includes nonselective beta-blockers, achievement of euthyroid state and eventually potassium supplementation. In conclusion, acute paralysis with hypokalemia should prompt physicians to evaluate thyroid function.

Severe sensorimotor polyneuropathy associated with vocal cord and pharyngeal weakness with distal myopathy (VCPDM) due to the p.S85C MATR3 mutation in an Italian patient

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Objective. To describe the first Italian patient affected by "vocal cord and pharyngeal weakness with distal myopathy" (VCPDM) due to *MATR3* c.254C > G (p.S85C) mutation, and to expand VCPDM phenotypic spectrum.

Methods. The proband underwent neurological evaluation, personal and family history investigation, lower limbs muscular magnetic resonance imaging, neurophysiological assessment, and muscle biopsy. Genetic analysis was performed by Next Generation Sequencing analysis of a panel of genes associated with distal myopathy and hereditary neuropathy.

Results. We detected the heterozygous c.254C > G, p.S85C *MATR3* mutation in a patient affected by progressive distal muscle weakness and hypotrophy, myalgias, dysphonia, dysphagia, respiratory impairment, and sensory abnormalities. Neurophysiological assessment revealed a severe sensorimotor polyneuropathy. Variation of fiber size, central nuclei, and non-rimmed vacuoles were evident at muscle biopsy.

Conclusions. This finding extends *MATR3*-associated VCPDM phenotypic spectrum and suggests considering *MATR3* analysis in suspected congenital polyneuropathies with odd features, including dysphonia, dysphagia, and respiratory insufficiency.

Technical tip: histopathological diagnosis of sIBM made easy after the re-orientation of the muscle biopsy

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Background. The histopathological diagnosis of sporadic inclusion body myositis (sIBM) represents a challenge because the pathology can be easily missed. The presenting case is of interest because the diagnostic alter-

ations were detected after the re-orientation of the original muscle biopsy.

Case description. A 75-year-old male patient underwent a forceps muscle biopsy of gastrocnemius muscle to confirm the clinical diagnosis of sIBM based on the typical distribution of muscle weakness and muscle atrophy, which developed slowly, over the course of 5 years, were asymmetric, of proximal-distal type in the lower limbs and predominant distal in the upper limbs. At the time of the last examination, the patient was unable to flex interphalangeal joints and had severe muscle weakness in hand extensors and flexors as well. He was previously surgically treated for stenosis of the lumbar part of the spinal canal without any relief. EMG was myopathic, creatine kinase was normal. Muscle biopsy demonstrated relatively few muscle fibers (cc. 50), longitudinally oriented and occasional mononuclear inflammatory cells. Rimmed vacuoles were not found. The specimen was cut in a different plane: rimmed vacuoles, with p62 positive inclusions, CD8+ lymphocytes invading non-necrotic muscle fibers and hypertrophic and atrophic muscle fibers were found, most of them cut perpendicularly. Electron microscopy revealed filamentous inclusions in occasional nuclei and in the cytoplasm.

Conclusions. A diagnostic yield of a single muscle biopsy may be increased by simple maneuver- reorientation of muscle biopsy. The presented case also illustrates the importance of muscle biopsy in avoiding unnecessary surgical interventions.

A novel AIFM1 missense variant associated with exercise intolerance and deafness

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Apoptosis Inducing Factor Mitochondria Associated 1 (AIFM1) is a mitochondrial oxidoreductase with different role in cell pathways, ranging from respiratory chain assembly, to cell death programmes. Pathogenic variants in the *AIFM1* gene have been associated with four neurological diseases such as the Cowchock syndrome (CMTX4), the X-linked deafness-5 (DFNX5), the combined oxidative phosphorylation deficiency 6 (COXPD6),

and the spondyloepimetaphyseal dysplasia with hypomyelinating leukodystrophy (SEMDHL).

Here we report a 17-year-old boy with a mild form of DFNX5 associated with clinical and histological myopathic features, harbouring a novel missense variant in *AIFM1*. He presented exercise intolerance since early childhood, and at age 7 he was diagnosed with a bilateral auditory neuropathy (deafness), treated with hearing aids.

Laboratory investigations, including serum CK and lactic acid were normal. Brain MRI at age 7 and muscle MRI at age 16 did not show any abnormality. An extensive electrophysiological study at age 17 ruled out a peripheral neuropathy. Muscle biopsy performed at age 11, showed myofibrillar texture abnormalities, such as moth eaten fibres and wiped out areas. Activities of the OXPHOS enzymes were normal, while further studies on apoptosis on muscle tissue are ongoing. Whole-exome sequencing (WES) revealed a missense hemizygous mutation in *AIFM1*, c.1552A > G (p.Lys518Glu), not previously reported in public databases.

In conclusion, this case further expands the clinical phenotype associated with *AIFM1* gene mutations.

Megaconial congenital muscular dystrophy due to novel CHKB mutations

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Megaconial congenital muscular dystrophy (CMD) is a rare form of congenital muscular dystrophy due to recessive mutations in *CHKB* gene, encoding Choline Kinase Beta. Since now only few cases have been described, mainly in Asian population.

We described a 6-year-old boy who came to our attention for cognitive impairment and slowly progressive muscular weakness. He was the first son of non-consanguineous healthy parents coming from Sri Lanka. Neurological examination showed proximal weakness at four limbs, weak osteotendinous reflexes, Gowers' manoeuvre and waddling gate. Creatine kinase levels were mildly increased. EMG and brain MRI were normal.

Muscle biopsy on quadriceps showed a dystrophic pattern with nuclear centralization and connective tissue

increase. Histological and histochemical staining were suggestive for subsarcolemmal localization and dimensional increase of mitochondria. Ultrastructural analysis confirmed the presence of enlarged (“megaconial”) mitochondria.

Direct sequencing of *CHKB* identified two novel defects: the c.1060G > C (p.Gly354Arg) substitution and the c.448-56_29del intronic deletion, segregating from father and mother, respectively. Interestingly, subclon-

ing of RT-PCR amplicons from muscle RNA showed that c.448-56_29del results in the partial retention (14 nucleotides) of intron 3, altering physiological splicing and transcript stability.

This report confirms the importance of considering *CHKB* mutations in the differential diagnosis of patients presenting with muscular dystrophy and mental retardation. Molecular analysis and muscle biopsy were fundamental for the diagnostic process.

ABSTRACTS OF POSTER COMMUNICATIONS

(in alphabetical order of the first Author)

Session 1

Care for adults with Duchenne muscular dystrophy (DMD): a single centre experience

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Adults with DMD are a highly vulnerable population. They are living longer thanks to the improvements of the standard of care but they also experience increasingly complex health issues. To date, there is a paucity of published natural history data and a lack of evidence for managing such complex patients, as recently highlighted by a Consensus document from the UK Adult North Star Network.

We present a single centre cross-sectional study on adults with DMD aged > 30 years who are being followed at our Neuromuscular Centre in Turin.

Currently, we are following 14 patients with DMD over their thirties (age range: 30 years 4 months - 47 years 10 months). Seven/14 patients are 30-35 years old, and 7/14 are older than 35 years, with 3 out of 7 aged > 45 years. All patients are living with their parent(s) but three who are living in a residential facility and one who is living independently (supported by a caregiver). Data on musculoskeletal, cardiac, respiratory, nutritional/gastro-intestinal function will be presented. Data on concomitant neurological (in particular epileptic) and psychiatric aspects will be presented alongside, as well as related management issues in terms of pharmacological treatments.

Discussion. Our data confirm the complexity of the multidisciplinary care of patients living with DMD in adulthood. Concomitant psychiatric conditions are frequent, and their pharmacological treatment challenging, especially considering cardiac comorbidities. Management is often based on personal clinical experience. Larger natural history studies and evidence based guidelines on this topic are strongly required.

Becker Muscular Dystrophy and 7q11.23 microduplication syndrome in a boy with developmental delay, bicuspid aorta and interatrial septum defect

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Becker muscular dystrophy (BMD) is a genetic disorder with X-linked recessive inheritance, caused by mutations of Dystrophin gene located at Xp21.2. It typically presents with gradually progressive muscle weakness. Developmental delay can be a manifestation of dystrophinopathies, and the etiology is a debated and investigated topic. 7q11.23 microduplication syndrome is a rare syndrome resulting from the partial duplication of the long arm of chromosome 7 characterized by a highly variable phenotype with mild to moderate intellectual delay, speech disorders, and distinctive craniofacial features. We describe a 7-year-old boy with BMD, who presented with developmental delay, bicuspid aorta and interatrial septum defect. At the presentation the serum creatine kinase level was markedly elevated (1046 U/L). Multiplex ligation-dependent probe amplification revealed an exons 48-deletion in the *DMD* gene. The presence of additional features prompted us to request a cgh array test that revealed a paternal 1.1 Mbp duplication in 7q11.23 region (72,856,430-73,985,812). The father has an intellectual disability too which has never been evaluated by neuropsychiatrist. To our knowledge this is the first case described with the association of BMD and 7q11.23 microduplication syndrome. The case highlights the diagnostic importance of cgh array test in individuals with developmental delay and congenital anomalies and its essential role in excluding other genetic causes of developmental delay/intellectual disability in dystrophinopathies.

Cerebral alteration patterns in children with Duchenne muscular dystrophy: a machine learning approach on magnetic resonance images

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Introduction. Cognitive and behavioral difficulties (i.e. Autism spectrum Disorder, ASD) are described in DMD patients. Different expression of dystrophin isoforms in specific brain areas may play a role in these comorbidities but few imaging data are reported in literature.

The aim of this study is to identify DMD specific brain abnormalities through a machine learning approach.

Materials and methods. 18 boys with DMD (age = 11.0 ± 3.6 yo; IQ = 72.3 ± 16.6 ; ASD diagnosis n = 5) and 18 controls (age = 9.5 ± 4.1 yo; IQ = 72.1 ± 22.3 ; ASD n = 5) underwent a Magnetic Resonance (RM) scan session with T1 and diffusion (DTI) sequences. Thickness of 360 cortical regions, volume of 40 brain structures, fractional anisotropy (FA) and mean diffusivity (MD) of 48 regions in the middle of the main fibre bundles were extracted from images.

All features were corrected for age, IQ and ASD diagnosis using a linear model. Group classification was performed using a linear SVM algorithm using a balanced leave-one-out cross validation procedure. Feature analysis was performed on the basis of the corresponding forward model weights.

Results. the linear classifier significantly discriminates between DMD patients and controls with accuracy = 97.2% ($p < 0.0005$) and AUC = 99.7% ($p < 0.0002$). The feature weights analysis shows that the discriminative information concentrates in the DTI derived measures (23 /25 ROI weights) and usually report a reduction (in FA/TR/thickness/volume) in DMD patients with respect to the control group (22/25 ROI weights). Moreover, the most selected ROIs refer to the cerebellum (cerebellar peduncles), the brain stem (medial lemniscus, inferior part of the corticospinal tract), the cingulum, the fornix and the superior fronto-occipital fasciculus.

Discussion. Machine Learning approach allows to identify brain abnormalities specifically associated with DMD, i.e. not caused by a comorbid condition.

Detection of dystrophin isoforms transcripts in human adult control brain using *in-situ* RNA analysis

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Duchenne muscular dystrophy (DMD) is an X-linked neuromuscular disease due to pathogenic variants in the *DMD* gene. DMD often is associated with cognitive and neuro-behavioural co-morbidities, which pathogenesis and genotype-phenotype relationship are only partially understood. Multiple *DMD* isoforms, differentially affected based on the mutation site, play a role in these co-morbidities, based on their moderate (Dp427, mainly muscle), prominent (Dp71) or exclusive (Dp140) brain expression.

We used two RNAscope® ZZ probes which recognize either the full-length Dp427 transcripts (exons 37-42) or all the *DMD* transcripts (exons 63-75). BaseScope® ZZ probes were also designed to specifically detect and localize the Dp427b, Dp427p2, Dp140, and Dp71 *DMD* isoforms. Real-time PCR was performed to validate the results. Sections from normal adult human formalin-fixed cerebellum and temporal lobe were used for the analysis.

Both RNAscope probes clearly showed the expression of *DMD* transcripts in cerebellum (molecular, granular, Purkinje, white matter) and temporal lobe (molecular, granular, pyramidal) tissue layers, including blood vessels. BaseScope® assay allowed discrimination of *DMD* isoforms and visualization of Dp427b, Dp427p2, Dp140, and Dp71 transcripts in both brain areas.

Here we demonstrate that the *in-situ* RNA hybridization approach has high sensitivity in detecting both full length and short dystrophin isoforms, and low abundant transcripts in fixed brain tissues.

The human brain expression map of the multiple dystrophin isoforms will help to define the regional and cellular pattern of *DMD* expression and may contribute to the understanding of the *DMD* brain co-morbidities.

A novel *DMD* gene splice-site variant in an Italian boy with Becker muscular dystrophy: a clinical and genetic study

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Background. Becker muscular dystrophy (BMD) is a dystrophinopathy caused by mutations in *DMD* gene which allow production of a partially functional protein, thus justifying the milder phenotype typical of the disease.

The molecular diagnostic process starts with the search of large gene deletions or duplications, and, when negative, it proceeds with the sequence of the entire *DMD* gene.

Case description. We studied a 26 years-old patient diagnosed at the age of 5 years-old with BMD. At the first evaluation, proximal muscular weakness at lower limbs, mild hypotrophy of pectoralis muscles and calf muscles pseudohypertrophy were detected. Current neuromotor assessment remained stable, however patient developed hypokinetic cardiomyopathy. Diagnosis was supported by immunohistochemical analysis showing faint dystrophin expression in muscle tissue. MLPA analysis did not show any major rearrangement on *DMD*.

Results. NGS analysis revealed a novel nucleotide intronic substitution *DMD:NM_004006:exon15:c.[1705-11A>G]:p.[?]* which affects a splice site. RNA analysis performed on muscle tissue showed expression of two different splice isoforms. The first one uses the splice site variant as a new acceptor site and generates an aberrant mRNA encoding a truncated protein. The second one consists in an "in-frame" splice of the exon 15. Segregation analysis confirmed the carrier condition of the mother.

Conclusions. Our study confirms the pathogenicity of the novel intronic variant *DMD:NM_004006:exon15:c.[1705-11A>G]:p.[?]* in *DMD* gene by demonstrating its direct effect at RNA level, and defines the genotype/phenotype correlation.

We also stress that the exon boundary should always be included in molecular analysis for an exhaustive diagnosis.

Antisense morpholino-based *in vitro* correction of a novel pseudoexon-generating mutation in the *SGCB* gene

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We report a 13 years-old patient presenting one year ago with incidental finding of high creatine-kinase levels (8413 IU/L). The patient played soccer at a competitive level and was completely asymptomatic, complaining only cramps after strenuous exercise. He did not show

weakness, fatigability, myalgias, myoglobinuria. Neurological examination was normal with exception for mild sural pseudohypertrophy. Cardiological evaluation was normal.

Muscle MRI showed fibroadipose substitution of glutei, paraspinal muscles, serratus and teres major.

Muscle biopsy displayed mild myopathic signs and moderate reduction of alpha-sarcoglycan levels at immunohistochemistry. A severe reduction of alpha- and beta-sarcoglycan was also confirmed by Western blot analysis.

NGS panel sequencing identified two mutations in the gene encoding for beta-sarcoglycan (*SGCB*): the previously reported known c.377_384dup microduplication and a novel T > C transition located within a putative pseudoexon. The latter variant activated the inclusion of a cryptic sequence between Exons 2 and 3 in *SGCB* transcript. Interestingly we detected the same variant in a previously reported Italian LGMDR4 patient in which molecular testing had only detected the c.377_384dup insertion. Molecular studies in patient's tissues, including autopsic heart specimen, showed global reduction of *SGCB* mRNA and altered splicing at transcript level. The *in vitro* administration of an antisense morpholino sequence targeting the pseudoexon restored physiological splicing in patient's myoblasts.

Our findings prompt the analysis of a novel variant in suspected LGMDR4 patients with monoallelic *SGCB* variants and provides a further example of the efficacy of morpholino antisense technology for the correction of splicing molecular defects.

Two cases of autosomal dominant Ullrich congenital muscular dystrophy due the same *de novo* mutation in the *COL6A3* gene

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Ullrich congenital muscular dystrophy (UCMD) is caused by mutations in *COL6A1*, *COL6A2* or *COL6A3* gene, leading to collagen VI deficiency. Either recessive (more frequent) or dominant inheritance is reported. Clinical-pathological hallmarks of UCMD include distal hyperlaxity, proximal joint contractures, early-onset rapidly progressive scoliosis, and respiratory failure. Muscle pathology is characterized by prominent interstitial fibrosis.

We describe a patient who came to our observation at the age of 11.5 years, for a picture characterized by early

tendon retractions, kyphoscoliosis, respiratory insufficiency (FVC 52%). Symptoms started at the age of 7-9 months; the child could not maintain the sitting position and never walked alone so the patient underwent a muscle biopsy, which showed a severe pattern of interstitial fibrosis. CK values were normal. There was no cardiac involvement. *COL6A1* and *COL6A2* gene analysis was negative.

Over the years, muscle condition remained stable, while the vital capacity has progressively deteriorated. He died at 25 years 9 months of acute respiratory failure.

Trio whole exome sequencing identified a *de novo* variant c.6210+1G>A at the 5' splice site of intron 16 of the *COL6A3* gene. This LoF variant, classified as pathogenic (VCV0000949S6.5), has already been reported in literature. We identified an additional case in a 4-year boy with decreased fetal movement, neonatal respiratory distress, bilateral cryptorchidism. Muscle-skeletal symptoms are present as scoliosis, adducted thumb, kyphoscoliosis, hip dysplasia hyperextensibility at wrists, central hypotonia and no cardiac involvement. These cases expands the number of patients with autosomal dominant UCMD, due to *de novo* mutation.

Oculo-pharyngeal muscular dystrophy: phenotypic and genotypic studies in Abruzzo

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Oculo-pharyngeal muscular dystrophy (OPMD) is a late-onset, inherited muscle disorder, characterized by progressive ptosis, dysphagia and variable proximal limb weakness. The highest prevalence is reported in French Canadians (1:1000) and Bukhara Jews (1:600). Few Italian cases have also been reported. OPMD is caused by short (GCN)₁₁₋₁₇ expansions in the polyadenylate-binding protein nuclear 1 gene (PABPN1).

We summarized the neurophysiological and genetic findings of 17 OPMD patients born in Abruzzo, belonging to 11 unrelated families.

In our cohort, age at onset was between 42 and 74 years (mean 57.5). The M/F ratio was 1.125:1. Family history was positive in 15 patients. As expected, ptosis was the most common initial complaint. There was a 5.8-year mean delay before the onset of a second symptom, which was dysphagia in 82.4% of cases. External ophthalmoplegia was present in 64.7% of patients. Two siblings presented cognitive impairment. Genetically, we identified four genotypes, including two GCN₁₁ homozygous patients. Mean age at first evaluation was 67.4 and

mean age at genetic screening was 69.4. Creatine kinase levels were mildly elevated in seven patients. Electromyography, performed in seven patients, showed myopathic features in four cases. Five patients had ptosis surgery and one patient reported cricopharyngeal myotomy.

According to our results, OPMD has an estimated minimal prevalence of 1.32 per 100.000 persons in Abruzzo. A disease cluster can be hypothesized in Caramanico, where OPMD prevalence is about 0.42%. Despite rapid diagnosis through *PABPN1* gene screening, OPMD is yet under-recognized and confirmed after several years from symptoms onset.

Disease characterization of ambulant patients with Becker muscular dystrophy: histopathological, functional and imaging data from Givinostat trial cohort

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Becker muscular dystrophy (BMD) is characterized by variable disease severity and progression, prompting the identification of biomarkers for clinical trials. We used data from a recently completed Phase II study to provide a comprehensive evaluation of a cohort of patients with BMD, and assessed correlations between histological and magnetic resonance imaging (MRI) markers with muscle function and strength. Eligible patients were ambulatory males with BMD aged 18-65 years (200-450 m on 6 minute walk test). The following were measured: function tests, strength, fat-fraction quantification using chemical shift-encoded MRI (whole thigh and quadriceps), and fibrosis and muscle fiber area (MFA) of the brachial biceps. Of 70 patients screened, 51 entered the study. There was substantial heterogeneity between patients in muscle morphology (histology and MRI), with high fat replacement. Total fibrosis correlated significantly and mostly moderately with all functional endpoints, including both upper arm strength assessments (left and right elbow flexion Rho -0.574 and -0.588, respectively [both $p < 0.0001$]), as did MRI fat fraction (whole thigh and quadriceps), e.g., with four stair climb velocity -0.554 and -0.550, respectively (both $p < 0.0001$). Total fibrosis correlated significantly and moderately with both MRI fat fraction assessments (0.500 [$p = 0.0003$] and 0.423 [0.0024], respectively). In

this BMD cohort, micro- and macroscopic morphological muscles parameters correlated (albeit moderately) with each other and with functional parameters, potentially supporting the use of MRI fat fraction and histology as surrogate outcome measures in patients with BMD, although additional research to validate this is required.

Evaluation of 6MWT as functional measure in Becker muscular dystrophy

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Aim of the study. To describe and analyse long term functional changes in Becker muscular dystrophy (BMD) through a commonly used outcome measure in neuromuscular diseases, the 6-minute walk test (6MWT).

Materials and methods. We selected patients coming from “Azienda Ospedale-Università di Padova” who have a molecular confirmed diagnosis of BMD. Our patients were followed up for at least 1 year by evaluating motor function through 6MWT and also North Star Ambulatory assessment (NSAA). We used a modified version of 6MWT specifically validated for DMD.

Results. Our cohort was composed of 105 subjects, of whom 99 patients could perform 6MWT at baseline. We divided patients according to mutational groups. The shortest distances were registered in the “del 45-48” group, (mean distance was $330.8 \text{ m} \pm \text{SD } 178.8 \text{ m}$), and the “del 45-47” group, (mean distance was $324.8 \text{ m} \pm \text{SD } 142.9 \text{ m}$).

The longitudinal study included a mean number of $5.25 (\pm 2.95)$ clinical examinations for each patient and the mean follow up was 4.66 years (± 3.0 years).

Longitudinal data showed a statistically significant yearly decrease in walked distance in “del 45-48”, “del 45-47”, and “del 48-49” groups. This decrease is larger if we only consider patients with a worst baseline muscular function (NSAA < 33).

We considered the comparison between the distances covered between the first and last 3 minutes of 6MWT as an indicator of fatigability. In the overall BMD cohort there was a significant decrease in distance between the two halves of the test, of $-3.0 \pm 18.5 \text{ m}$ ($p = 0.0005$). This difference was larger in patients with baseline NSAA ≤ 32 ($-5.3 \pm 10.3 \text{ m}$, $p < 0.0001$).

Conclusions. We provide cross-sectional values for the 6MWT in a large BMD population, and demonstrate significant yearly changes in longitudinal evaluations, and a tendency to decreasing speed during the test, suggestive of fatigability.

An integrative splicing predictor pipeline to prioritise DMD deep intronic variants

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Deep intronic single nucleotide variants (SNVs) are the most elusive DNA variants for NGS. Thus, defining their pathogenic role remains challenging and many genetic conditions remain unsolved. Some of deep intronic variants could lead to aberrant splicing, resulting in partial or full pseudo-exon (PEs) inclusion, mainly due to the activation of cryptic intronic acceptor and/or donor splice sites and the alteration of sequence motifs recognized by enhancer or silencer splicing factors.

Here, we tested a computational approach to evaluate splicing involvement of DMD deep intronic SNVs annotated in the Leiden Open Variation Database (LOVD).

To prioritize our set of variants based on their probability to be involved in PEs formation, we sequentially applied four different prediction tools (SpliceAI, NNSplice Predictor, HSF and SFMap). We divided the collected LOVD variants into two groups, TRAINING (variants with known RNA effect) and TESTING (variants with unknown RNA effect), which were used respectively to validate and test our pipeline. For TRAINING group, we confirmed involvement of 77% of variants in PEs inclusion. Interestingly, we found that 72% of TESTING variants are involved in alternative splicing leading to PEs inclusion.

Overall, we believe that this pipeline could be useful to confidently predict the effect of specific SNVs on alternative splicing and PEs formation, thus providing good indication for NGS variants prioritization and transcriptomic studies in muscular biopsy.

Session 2

COVID-19 vaccine and dermatomyositis: is there an association?

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The etiology of dermatomyositis is unknown but immune dysregulation plays a key role.

A 68-year-old man presented with a 1-month history of skin rash, myalgia and symmetrical proximal limb weakness. He developed these symptoms about three weeks after the second dose of Vaxzevria. On examination, he showed a diffuse facial, scalp, arm and trunk rash with periorbital edema. No Gottron papules were detected. Creatine kinase levels were markedly increased. Electromyography was normal, whereas muscle biopsy revealed a perivascular mixed cell infiltrate. Based on clinical features, elevated muscle enzymes and muscle biopsy, a diagnosis of dermatomyositis was established. A full-body CT scan, performed in order to exclude a connection with malignancies, appeared unremarkable. The patient showed a gradual improvement of symptoms after treatment with intravenous methylprednisolone 80 mg for three days, then transitioned to oral prednisolone 50 mg.

To the best of our knowledge, this is the first case of new-onset dermatomyositis after COVID-19 vaccination. Dermatomyositis occurring after vaccination is a well-recognized phenomenon and may be attributable to homology between vaccine components and muscle antigens, triggering an autoimmune response. Moreover, dermatomyositis has been recognized as a manifestation of COVID-19-induced muscle disease. It has been hypothesized that SARS-CoV-2 may transfer its genetic material into the muscle fibers, thus triggering a T cell-mediated viral response leading to muscle damage. In addition, three different T cell receptor epitopes "highly specific" for SARS-CoV-2 have been detected in dermatomyositis patients, reinforcing the hypothesis of molecular mimicry.

Characterization of p.N1180I sodium channel mutant associated to myotonia and myopathy in Italian patients

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In this work, we studied a novel mutation in *SCN4A* gene (p. N1180I), identified in two Italian families showing a peculiar phenotype characterized by the association of myopathy and myotonia (Fusco et al., *Brain Dev.* 2015; Rigamonti et al., *Neurol Sci.* 2021).

The mutation N1180I was introduced into the pRc/CMV plasmid containing the cDNA encoding wild-type (WT) human Nav1.4 channels. Whole-cell sodium currents were recorded with patch-clamp technique in HEK293 cells transfected with WT or N1180I.

Cells transfected with 0.5 µg/ml cDNA of N1180I

did not express any current ($n = 15$), in contrast to 100% of WT-transfected cells. Increasing N1180I cDNA to 1 µg/ml allowed recording of sodium currents in 15 out of 98 patched-cells. Maximum current amplitude from I-V curves was reduced for N1180I (-229 ± 38.5 pA, $n = 5$), compared to WT (-3959 ± 615 pA, $n = 17$, $p < 0.005$). Decay of N1180I currents was significantly slowed. The voltage-dependences of activation and fast inactivation were significantly positively shifted by about 14 mV and 9 mV, respectively.

The fast inactivation impairment by N1180I suggests a gain of function of Nav1.4 channels, in accord with occurrence of myotonia in the patients. However, the reduction of expression efficiency and maximum current amplitude, together with the positive shift of activation, suggest a loss of function more compatible with the presence of myopathic traits in the patients. More studies are needed to better understand the mechanisms allowing occurrence of both myotonia and myopathy in the same patient (Supported by Grant 2017-2018 from the University of Bari).

Mutations associated with hypokalemic periodic paralysis: from hotspot regions to complete analysis of *CACNA1S* and *SCN4A* genes

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Background. Familial periodic paralyses (PPs) are inherited disorders of skeletal muscle characterized by recurrent episodes of flaccid muscle weakness. PPs are classified as hypokalemic (HypoPP), normokaliemic (NormoPP) or hyperkalemic (HyperPP) according to the potassium level during the paralytic attacks. HypoPP is an autosomal dominant disease caused by mutations in the *CACNA1S* gene, encoding for Cav1.1 channel, (HypoPP-1), or *SCN4A* gene, encoding for Nav1.4 channel, (HypoPP-2).

Methods. In the present study, we included 60 patients with a clinical diagnosis of HypoPP. Fifty-one (85%) patients were tested using the direct sequencing (Sanger method) of all reported HypoPP mutations in *CACNA1S* and *SCN4A* genes; the remaining 9 (15%) patients were analyzed through a next-generation sequencing (NGS) panel, including the whole *CACNA1S* and *SCN4A* genes, plus other genes rarely associated to PPs.

Results. Fifty patients resulted mutated: 38 (76%) cases showed p.R528H and p.R1239G/H *CACNA1S* mutations and 12 (24%) displayed p.R669H, p.R672C/H, p.R1132G/Q and p.R1135H *SCN4A* mutations. Forty-one mutated cases were identified among the 51 patients managed with Sanger sequencing, while all the 9 cases directly analyzed with the NGS panel showed mutations in the hotspot regions of *SCN4A* and *CACNA1S*. Ten out of the 51 patients unresolved through the Sanger sequencing were further analyzed with the NGS panel, without the detection of any mutation.

Conclusions. Hence, our data suggest that in HypoPP patients the extension of genetic analysis from the hotspot regions using the Sanger method to the NGS sequencing of the entire *CACNA1S* and *SCN4A* genes does not lead to the identification of new pathological mutations.

A very late onset AChR and MuSK double positive myasthenia gravis

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AChR and MuSK double positive myasthenia gravis has been rarely reported. Generally, it occurs in children and adults after thymectomy or immunotherapy, two young female patients has been described as double positive since the onset of the disease. We report herein a man with a very late onset myasthenia gravis (86-year-old) and coexistence of both antibodies at the time of the diagnosis with a favourable clinical outcome. Despite the presence of MuSK antibodies, he manifested no bulbar symptoms but side effects related to low dose pyridostigmine were evident. Hence, double positivity should be considered also in elderly. We suggest to detect AChR and MuSK antibodies at the time of diagnosis. Other cases of AChR and MuSK double positive myasthenia gravis could allow a better definition of this condition.

Congenital myasthenia associated with new variant of the *prepl* gene

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Congenital myasthenic syndromes (CMS) are genetic disorders characterized by impaired transmission at the motor endplate. Clinically, these forms present with prevalent weakness of the axial muscles (hypotonia at onset) and bulbar muscles (ptosis, ophthalmoplegia, dysphagia, facial weakness). Fluctuations of symptoms, facial dimorphisms and distal weakness are other common features. CMS may respond to treatment with drugs enhancing the neuromuscular transmission and differential diagnosis with congenital myopathies is fundamental.

The *PREPL* gene, responsible for the autosomal recessive form of CMS22, belongs to the prolyl-oligopeptidase subfamily of serine peptidases. *PREPL* is localized in the cytosol where it is involved in exocytosis processes.

We report an 11-year-old patient with CMS, harboring a novel homozygous variant in *PREPL*. At onset, the patient presented with neonatal hypotonia followed by rhinolalia, bilateral ptosis and dysphagia. Muscle biopsy revealed myopathic changes with selective hypotrophy of type II fibers, in absence of specific characteristics.

We performed a custom NGS panel for congenital myopathies/myasthenic syndromes which revealed the homozygous (NM_001374276.1): c.950dup (p.Glu318Argfs*6) variant in *PREPL*. This insertion determines a premature stop codon, likely leading to non-sense-mediated mRNA decay. The variant is not reported in GnomAD and ClinVar, and is predicted pathogenetic by *in silico* tools.

The repetitive stimulation confirmed an alteration of the neuromuscular transmission. The patient started a treatment with pyridostigmine, which was stopped due to allergic reaction and replaced by salbutamol. This resulted in a global improvement of the generalized hypotonia and dysphagia. However, ptosis and rhinolalia remained severe, with perturbation of speech.

This case underlines the importance of genetic characterization for proper clinical management and specific therapeutic strategies.

Rituximab in refractory Myasthenia Gravis: what we learned after 10 years. A single centre experience

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Myasthenia Gravis (MG) is characterized by muscle fatigue, determined by autoantibodies against components

of neuromuscular junction, like Acetylcholine Receptor (AChR) and Muscle Specific Kinase (MuSK). Therapies differ according to clinical severity, including symptomatic treatment, immunomodulant approaches and immunosuppressants. Rituximab (RTX) is a “target” immunosuppressant agent against CD20 antigen, determining selective depletion of B lymphocytes with a long-lasting reduction of humoral immune response. It is increasingly used in clinical practice as an off-label treatment of refractory MG. High efficacy has been demonstrated in anti-MuSK MG, though there is also evidence of efficacy in anti-AChR and seronegative MG. Between 2009 and 2020, 12 patients with generalized refractory MG referring to our Unit have been treated with RTX (cycles of 1000 mg IV repeated after two weeks). Among them (9 females and 3 males) 6 had anti-MuSK MG and 6 anti-AChR MG; 3 of these patients had thymoma surgically removed. Efficacy duration of a single cycle ranged from 6 months to 9 years. About 70% of patients substantially reduced dosages of immunosuppressive treatments within one year. At most recent follow up (2021) 6 patients were in Complete Stable Remission, 1 in Pharmacological Remission and 5 in Minimal Manifestation-3 status, according to MGFA Post Interventional scale. None of our patients developed myasthenic crisis or required rescue therapies since the introduction of RTX. Only one severe drug-related, but reversible, adverse event (hypertensive crisis) was observed. Our experience confirmed RTX as a safe and effective treatment for both anti-MuSK and anti-AChR MG patients.

Impact of COVID-19 and vaccines in Myasthenia Gravis: experience from an Italian cohort

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Background and aims. Since COVID-19 infection became a global public health problem, finding a treatment has been an emergency and vaccines are considered the only solution. In the last months, a big amount of data has been published on COVID-19 and vaccines and are currently available for the general population, but little is still known regarding patients with myasthenia gravis.

Methods. We performed a cross-sectional study among a cohort of patients with Myasthenia gravis attending to the Neuromuscular Clinic of the University Hospital “Paolo Giaccone” of Palermo. Patients underwent a telephonic interview through a dedicated questionnaire about COVID-19 infection, vaccinations, and their effects on MG.

Results. In our cohort 9 patients resulted positive to SARS-COV2 infection, 4 patients died for COVID-19, a patient worsened for MG, requiring respiratory support, whereas 3 patients were asymptomatic. Fifty-three patients completed the vaccination with minor side effects in 24 cases. Seventeen patients presented a worsening of symptoms.

Conclusions. The reduced number of adverse events in our population suggests that vaccines for SARS-cov2 are safe in myasthenic patients that could take advantage of vaccination avoiding life-threatening complications such as myasthenic crisis and COVID-19 pneumonia. The continuation of the regular and periodic clinical follow-up will provide us data on the real effectiveness of vaccine prevention in the myasthenic population.

Mutation of *LRSAM1* gene: a novel cause of congenital myasthenic syndrome

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Background. Congenital myasthenic syndromes (CMS) are hereditary neuromuscular junction disorders, due to defects of proteins involved in endplate development and function. Different CMS have no clear genetic cause yet, therefore many other genes will have to be discovered.

Cases description. We describe herein a 52-year-old woman, whose first fatigability symptoms manifested at the age of 43 years old. She complained of left fingers weakness, that progressively involved the other hand and pelvic girdle muscles, with difficulty to raising from a chair and climbing stairs. Besides, she presented sporadic episodes of double vision. Clinical examination revealed waddling gait, not possible on heels, positive Gowers sign, severe weakness of flexors and extensors finger muscles, mild weakness of bilateral iliopsoas muscle and pes cavus.

Results. Blood investigations, including serum CK, were normal. Electromyography evidenced a myopathic pattern. Ulnar nerve repetitive stimulation recorded no alteration, but single fiber electromyography showed increased jitter and blockings. AChR-Abs and MuSK-Abs were negative. Sequence analysis of CMS-related genes resulted surprisingly normal, while it was found a stop codon mutation of *Leucine Rich Repeat And Sterile Alpha Motif Containing 1* (*LRSAM1*) gene (c.1279C > T; p.Arg427Ter), encoding for an axonal membrane protein. Despite that, therapy with ephedrine was started with subsequent and progressive improvement of clinical manifestations.

Discussion and conclusions. To date, mutations of *LRSAM1* gene have been reported in Charcot-Marie-

Tooth type 2P. Our patient presented clinical and neurophysiological features of CMS.

This case highlights the opportunity to find new molecular basis for these disorders in order to better define their pathophysiology.

SARS-CoV-2 infection in myasthenic patients from Liguria

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Objective. Neuromuscular diseases (NMD) may represent a risk factor causing a more severe course and outcome of SARS-CoV-2 infection. Interestingly, we observed several cases of SARS-CoV-2 infection in Ligurian patients affected by Myasthenia Gravis from March 2020 to April 2021.

Methods. We collected data from 13 patients affected by Myasthenia Gravis, followed in different Ligurian hospitals. While eight patients had a mild course of SARS-CoV-2 infection, 5 patients had an unfavorable course causing the death of 4 patients and a prolonged life threatening hospitalization in one patient. We analyzed their MGFA class at the moment of the infection, the maximum MGFA class reached during their clinical history, and the previous number of myasthenic crisis. We also evaluated the age at the infection, the BMI and the number of comorbidities as independent risk factors for infection severity.

Results. As expected, age and elevated BMI are independent risk factors for poor outcome of Covid-19 in myasthenic patients (mean age 68,3 range 47-87 years; comorbidity rate overall 53.8%). Also having 1 or more comorbidities predicts a higher hospitalization rate (7/8 patients, 85.7%). Interestingly, the five patients with an unfavorable SARS-CoV-2 infection course had a moderate MGFA class at the moment of the infection, but almost all (80%) had previous myasthenic crisis and the average maximum MGFA class reached during the clinical history was significantly higher (MGFA = 4), compared with the group with a prompt recover (MGFA = 2); $p : 0.01$.

Conclusions. Among our neuromuscular patients, SARS-CoV-2 infection had a significant impact in particular in myasthenic patients causing the death of four of them and a long hospitalization in one. Despite My-

asthenia was well compensated at the moment of the infection, patients with previous myasthenic crisis and a higher MGFA maximum tended to have an unfavorable course. This correlation, already described in a large French study (Solé G et al. Impact of Coronavirus Disease 2019 in a French Cohort of Myasthenia Gravis. *Neurology* 2021) supports the hypothesis that autoimmune neurological diseases may be a risk factor for a severe course of SARS-Cov-2 infection.

Session 3

Severe progressive course in an NLSDM patient put on MCT dietary treatment

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A 29-year-old woman with Neutral Lipid Storage Myopathy (NLSDM) is presented.

Until 2015, she was asymptomatic except for elevated CPK. At 18 years, hyperCKemia suggested NLSDM diagnosis and sequencing analysis revealed a retrotransposon insertion in *PNPLA2* gene. *PNPLA2* encodes the lipase ATGL, which mutations cause NLSDM onset.

In the following years, the patient has been experiencing muscle weakness in both arms, shoulders, and hands, then extended to lower extremities. Calves MRI showed lipid accumulation. At 27 years, she was put on a diet with 30 grams per day of MCT oil and 15 grams of natural fat. After beginning MCT diet, the CPK lowered, from 2640 U/l to 1424 U/l. Nevertheless, muscle weakness did not improve, as showed by GSGC score performed in 2020: Walking 10 Meters = 10 seconds; Climbing Stairs = 13 steps up = 8.10 seconds. 13 step down = 6.40 seconds; Raising from seated floor position with no hands = 2.76 seconds; Getting out of chair = .61 seconds (< less than 1 second).

Following parents' request, we planned a recruiting study for NLSDM, as previously described. We suggested performing a new MRI and skin biopsy. While the skin biopsy showed only a slight oedema, muscle MRI highlighted advanced fat substitution in both upper and lower extremities.

In this patient, no beneficial effects on myopathy progression were observed after MCT diet, probably due to complete loss of ATGL production. We reported several cases in a NLSDM registry and this patient represents an NLSDM spectrum severe example.

The role of muscle biopsy: a 15 years single center experience

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Background. Muscle biopsy is considered to be the gold standard test for diagnosis of muscle disease. It is usually indicated to evaluate abnormal clinical and/ or laboratory findings suggestive of myopathy, such as HyperCKemia, myalgia, exercise intolerance, family history of myopathy, muscle weakness, and abnormal electromyography (EMG).

Methods. We retrospectively reviewed 889 consecutive muscle biopsies performed at Center for Neuromuscular disease between 2005 and 2020. We collected several patient information including laboratory data, neurological examination, genetic and biochemical test.

Results. The clinical reason for performing the muscle biopsy was myalgia in 32% of cases, muscle weakness in 50.4%, muscle atrophy in 4.1% and at least 1 episode of Rhabdomyolysis in 5.1%, while 9.1% of patients had chronic CK serum elevation and 4.4% had a past diagnosis of myopathy.

Muscle biopsy led to a unique diagnosis in 42.2% of cases, which the most frequent were inflammatory disease and dystrophic forms.

The Area Under the Curve (AUC) for prediction of a specific biopsic diagnosis was 0.63 (0.59-0.68) for patient with weakness, 0.57 (0.53-0.61) for patients with Hyperckemia and 0.63 (0.59-0.68) for patient with myopathic EMG. The association of these 3 element results in an increase of the AUC (0.73, 0.68-0.77). A definitive diagnosis was obtained in only 21.5% of patients without specific a priori clinical suspicion.

Conclusions. Muscle biopsy remains a fundamental diagnostic test for the study of muscle pathologies, especially in patients with specific clinical signs. However, its role is less clear in patients with more subtle clinical elements.

Respiratory function in myotonic dystrophy type 1: a retrospective study

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Introduction. Respiratory insufficiency is one of the main causes of death in myotonic dystrophy type 1 (DM1). Predictive factors, rate of decline and the effects of ventilator support need to be further explored.

Objectives. To analyze respiratory function over time.

Methods. 175 adult patients with DM1 were subjected to arterial blood gas analysis, spirometry, cough measurements, nocturnal oximetry and respiratory muscle strength testing. Results were correlated with neuromotor function and coping strategies.

Results. At baseline 84 of 175 had normal respiratory function (median age 38 years, median BMI 23.9, median disease duration: 11 years); 24 were already on NIV (median age: 49 years, median BMI: 26.1, median disease duration: 21.5 years) and 67 received an indication to use NIV (median age: 49 years, median BMI: 25.8, median disease duration: 14 years). After a median time of 3.85 years, 43 patients were lost to follow-up; 9 of 84 required NIV; 16 patients initially on NIV kept using NIV; only 17 of 67 with the new NIV prescription were compliant.

Conclusions. Respiratory involvement affects almost 50% of patients with DM1 although typical respiratory symptoms may not be present. The majority required NIV and these were the most severely affected patients and having the longest disease durations and higher BMIs than the cohort having normal respiratory function. A minority (11%) required NIV during our observational period. Only 25% was NIV compliant and this was unrelated to the patients' coping strategies or to specific demographic or respiratory distinctive features.

Establishing biomarkers and clinical endpoints in myotonic dystrophy type 1 (END-DM1): Italian experience

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Background. Myotonic dystrophy type 1 (DM1) is characterized by a wide phenotypic variety. There is consensus about the need for multidisciplinary management of this disease, but there is still a need to harmonize procedures of assessment and to define the best outcome measures. END-DM1 is a multicenter, international, observational and prospective study proposed by DMCN. The NeMO Clinical Center in Milan is the Italian representative for this network.

Aims. to describe the NeMO's experience in screen-

ing, evaluating and collecting data along with difficulties and strengths in following END-DM1 procedures.

Methods. The protocol includes: clinical assessments (medical history, physical exam, vital signs and EKG), mobility and functional measures (10MWT, 6MWT, TUG, 4 stairs, timed supine-to-sit, step test, vHOT, pick-up coins, 9NHPT), measures of strengths (QMA, MMT, IOPI) and pulmonary function, PROMs (MDHI, EAT-10, Domain Delta questionnaire, WPAI:SHP, EQ-5D-SF, Walking Scale-12, DM1-Activ), cognitive function (Cog-state), biomarker and genetic assessments (blood and urine samples and muscle biopsy).

Results. We recruited 65 adult onset patients (44 females, age: 44 ± 13.57): 2 were wheel-chair bound, 7 had PM/ICD, 26 cataracts and 21 NIV. Age of first symptom: 22.66 ± 13.57 ; age at diagnosis 31.54 ± 12.45 ; grip myotonia was the most frequent symptom at onset (61/65) and hand weakness often preceded limb weakness. Only 4 patients reported cognitive symptoms.

Conclusions. This academic registry highlights the importance of providing appropriate evaluations by trained and dedicated staff in order to guarantee quality control of data entry in preparation for clinical trials while providing care according to patients' needs.

Cardiac magnetic resonance findings and outcome in type 1 myotonic dystrophy

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Heart disease is a determinant of prognosis in type 1 myotonic dystrophy (DM1). Cardiac imaging, possibly including cardiac magnetic resonance (CMR), is recommended, but there is limited information on CMR findings and their prognostic significance. All DM1 patients referred to our CMR laboratory between 2009-2020 (n = 34, 21 males, aged 45 ± 12) were retrieved. At the time of CMR, 90% had neuromuscular symptoms (duration 17 ± 13 years), 13(38%) had previous reports of atrioventricular block, 30(88%) of intraventricular conduction disturbances, 4(12%) of atrial fibrillation/flutter. At CMR, 5(15%) patients had left ventricular (LV) systolic dysfunction (LVEF < 50%) and 4(12%) a depressed right ventricular (RV) function (RVEF < 50%). Compared to age- and sex-specific reference values, 12(35%) showed a decreased LV end-diastolic volume index (LVEDVi), 7(21%) a decreased LV mass index (LVMI),

and 29(85%) a decreased LVMI/LVEDVi. Nine(26%) patients had mid-wall late gadolinium enhancement (LGE), and 14(41%) some areas of fatty infiltration. Native T1 in the interventricular septum (1.041 ± 53 ms) approached the upper reference limit (1.089 ms), and the extracellular volume was increased ($33 \pm 2\%$, reference < 30%). Over a median follow-up of 2.5(1.5-4.0) years, 2(6%) patients died for infectious and respiratory complications, 5(15%) underwent PM/ICD implantation and 4(12%) presented high-risk (Lown ≥ 4) ventricular ectopic beats (VEBs). Among CMR variables, high LVMI/LVEDVi emerged as univariate predictor of all-cause death (p = 0.044). At logistic regression, antero-septal wall thickness was associated with PM/ICD implantation (p = 0.028), LGE mass with high-risk VEBs (p = 0.026). In conclusion, DM1 patients display cardiac muscle hypotrophy, fibrosis and fatty infiltration at CMR. Such changes may anticipate the worsening of electrical disturbances.

A novel distal vacuolar myopathy caused by a large expansion of the *PLIN4* gene-clinical, histological and imaging data

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We formerly reported an Italian kindred with adult-onset autosomal dominant vacuolar myopathy with 19 affected individuals over four generations. Myopathology was characterized by rimmed autophagic vacuolation and distinctive immunohistochemical features including involvement of the ubiquitin-proteasome pathway. More recently, we identified the protein accumulating within the vacuoles and pinpoint, with the use of long-read sequencing, a large coding expansion in the *PLIN4* gene, member of the perilipins' family. The accumulation of this protein within the vacuoles and in the subsarcolemmal region of the affected fibers, coincides with the immunohistological activation of the key players of the autophagy pathway, notably p62/SQSTM1, NBR1 and WDFY3. We present here clinical, histological and muscle imaging data of 15 affected patients carrying the *PLIN4* gene expansion. Mean age at onset was 47.3 ± 10 years (range 30-66), with upper or lower limb distal muscle weakness as presenting symptoms in most of the patients. Disease progression was slow over the years, with around half of the patients developing a predominant scapulo-humeral-peroneal pattern of weakness. Five out of 15 (33.3%) patients were wheelchair-bound after a mean disease duration of 14 ± 6.6 years. No relevant heart involvement was observed. Rimmed

values were detected in all muscle biopsies taken from the patients. The extent of the histopathological changes varied between patients correlating with disease severity and *PLIN4* expansion entity. In conclusion, we clinically and histologically characterized a new vacuolar distal myopathy presenting in adult age, linked to a pathological expansion of the *PLIN4* gene.

Prevalent muscle involvement in two siblings with Glycogen Storage Disease type III

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Glycogen Storage Disease type III (GSDIII) is a rare autosomal recessive disease caused by deficiency of the glycogen debranching enzyme (AGL). Consequently, glycogen accumulates in the affected tissues, mainly damaging liver, muscles and heart (GSD IIIa); in a minority only liver (GSD IIIb). The onset is in infancy. However, the risk of hypoglycemia usually decreases with age, with progressive reduction in liver volume, during pubertal age. In adulthood, cirrhosis of the liver and/or hepatomas may appear, as well as the involvement of skeletal muscles and myocardium.

We describe two siblings, male and female, with GSDIII presenting with an early skeletal muscle involvement. *Male*: onset in the second decade, with difficulties in walking, climbing stairs and getting up from the floor, progressively worsening, associated to muscle weakness. Severe kyphoscoliosis. CK values up to 16 times the maximum normal values. Episodes of hypoglycaemia at 30 years; hepatosplenomegaly. Hypertrophic cardiomyopathy diagnosed at 43 years. LoA at 54 years. Over the years, worsening of general conditions, and increased functional limitation in daily activities. *Female*: onset of muscle symptoms at the same age; LoA at 43 years. No cardiomyopathy. CK values up to 17 times the maximum. Vacuoles at muscle biopsy, with modest glycogen accumulation; debranching enzyme deficiency causing the disease. Death at 49 years, for causes unrelated to the disease.

NGS analysis showed the homozygous variant c.1283G > A p.R428K in exon 10 of the *AGL* gene, which modifies the last nucleotide of the exon. This variant most likely affect the splicing, as SpliceAI assigns it a score of 0.72 for donor loss.

The cases here reported broaden the spectrum of GSDIII clinical presentation, confirming its clinical heterogeneity and intra-familial variability.

Natural history of skeletal muscle laminopathies: a 2-year prospective study

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Mutations in *LMNA* lead to skeletal muscle laminopathies (SMLs), a group of rare disorders characterized by skeletal and cardiac muscle involvement. To date, natural history of SMLs is not clarified yet, being mainly described by retrospective studies, reporting only major events.

We aimed to investigate the natural history of SMLs through a 2-year prospective study, including several clinical outcome measures.

Methods. Twenty-six SML patients were enrolled in the present study and assessed with the following tests: North Star Ambulatory Assessment scale (NSAA), timed tests, manual muscle testing, joint range of motion, six-minutes walking test (6MWT); respiratory evaluation including forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV₁); individualized neuromuscular quality of life (INQoL) questionnaires; cardiac evaluation collecting standard 12-derivations electrocardiogram, 24-hours Holter ECG monitoring and heart echo scan.

Results. At the baseline, clinical assessments significantly (p value < 0.05) correlated with SMLs phenotypes, showing a worst performance in Emery-Dreifuss muscular dystrophy 2 patients. The NSAA score significantly deteriorated (p value = 0.0005, mean change: 2.9 ± 0.4) during the 2-years follow up. The respiratory function through FVC (p value: 0.0086, mean change: 6.9% ± 1.4%) and FEV1 (p value: 0.0290, mean change: 6.7% ± 1.8%) significantly declined. Conversely, 6MWT and timed tests, did not significantly change. Similarly, elbow, knee and ankle joint range of motion resulted unchanged.

Conclusions. Disease progression of SMLs was shown with NSAA, FVC and FEV1 in a 2-year period, suggesting a slow decline of the motor and respiratory function in these patients.

Muscle MRI images in patients with chronic progressive external ophthalmoplegia

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Introduction. Progressive external ophthalmoplegia (PEO) represents the most common feature of mitochondrial disorders. When it occurs in isolation, it is defined “chronic progressive external ophthalmoplegia”(CPEO) while the combination of PEO and other features of neuromuscular and multisystem involvement (excluding CNS) is named “CPEO plus syndrome”. Clinical variability is broad even in individuals harbouring the same genotype. Recently, some studies focused the attention on muscle weakness, exercise intolerance, and muscular pain as features of mitochondrial diseases. However, fewer studies focused the attention on severity and distribution of muscle wasting and damage in PEO patients. Our aim is to analyse systemic muscles involvement with the use of muscle MRI.

Materials and methods. We enrolled patients diagnosed with CPEO or CPEO plus by clinical, biological and genetic tests, at Neuromuscular Centre of Careggi University Hospital, Florence. We analyzed T1-weighted sequences of the neck, shoulder girdle, paraspinal muscles, lumbar girdle, thighs, and legs, evaluating the severity of wasting and the grade of fatty tissue substitution.

Results. MRI images were taken from 7 patients (3 men); their age ranged between 23 and 72 years. Three patients (2 men, age 56-72yrs) had CPEO-plus; 2 harboured pathogenetic variants in *POLG*. In those individuals, MRI showed similar involvement of the axial, tight, and leg muscles. Studies of the remaining 4 patients, who are still awaiting molecular definition, were unremarkable.

Conclusions. MRI could be a useful and informative tool in the clinical evaluation of the general muscle involvement of CPEO patients.

This research project is funded by Tuscany Region.

Psychopathology and coping styles in patients with neuromuscular disorders: a follow-up study during the COVID pandemic

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Objective. To verify the change in the emotional and behavioural conditions of neuromuscular disorders patients' before and during the COVID-19 pandemic and to evaluate if the change was predicted by coping strategies.

Methods. We analyzed 43 participants – age range at first assessment 4-52 - out of 112 subjects recruited in the study. The emotional and behavioural conditions were assessed through standardized questionnaires: Youth Self Report (YSR), Adult Self Report (ASR), Child Behaviour Checklist (CBCL), Adult Behaviour Checklist (ABCL). The pre-pandemic coping strategies of both parents and patients were assessed through the New Italian Version of the Coping Orientation to the Problems Experienced questionnaire.

The relationship between coping strategies and psychopathological profiles was investigated through correlations, while the change in the patient's psychopathological profile was observed with repeated measures ANOVA. The predictivity of coping strategies on adaptation during pandemic was analyzed through linear regression's analysis.

Results. Patients' coping strategies are correlated with psychopathological level reported by caregivers pre pandemic. ABCL and CBCL scores reported a significant worsening in patients' general emotional-behavioral conditions during COVID-19, even though it's under clinical cut-off; whilst patients didn't perceive any variation in their well-being status.

The change has no causal relationship with the patients' coping strategies.

Conclusions. Pre pandemic, parents' perception of the patient's psychopathological level depends on the coping strategies used by the subject. Caregivers perceive a worsening of the patient's psychopathological level during the pandemic, but this is not predicted by the patient's pre-pandemic coping strategies.

Late-onset diffuse myalgias and multiple subarachnoid cysts. A case report

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We present the case of a 52 years old male patient that came to our attention for widespread myalgia, progressive thinning of muscles and muscle cramps mainly localized at the lower limbs, without significant weakness, beginning two years ago. A positive family history for myotonic dystrophy type 2 (father) was reported. He had also previously performed a brain MRI for recurrent cephalalgia, revealing multiple, large, mainly temporo-occipitally localized subarachnoid cysts along with diffuse leukodystrophic involvement of both supra and infratentorial white matter. Based on clinical, anamnestic and imaging data, both analysis of expansions of the CCTG repeat in the *CNBP* gene for DM2 and an NGS analysis panel for leukodystrophies were performed; the patient tested positive for DM2 and a rare variant of unknown significance (allelic frequency 0.00026) associated with autosomal dominant microangiopathy and leukoencephalopathy was identified in the *COL4A1* gene (c.2126C > T).

Session 4

Quality of life assessment in adult spinal muscular atrophy patients treated with nusinersen

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Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by loss of bulbar and spinal motor neurons due to defective production of SMN protein. Nusinersen, able to restore SMN transcription levels, had recently revolutionized the approach to SMA determining motor function improvement and prolonged survival.

Here, we retrospectively evaluated quality of life (QoL) in a large multicenter cohort of adult SMA patients during nusinersen treatment.

We included adult patients who started nusinersen treatment in adulthood. QoL was rated by the Individualized Neuromuscular Quality of Life (INQoL) questionnaire. Concurrent motor function evaluation included the Hammersmith Functional Motor Scale Expanded (HF MSE), the Revised Upper Limb Module (RULM), the six minutes walking test (6MWT).

189 completed questionnaires were collected during a 14 months' treatment period. 78 patients were included (7 SMA2 and 69 SMA3 and 2 SMA4) with mean disease duration at first nusinersen administration of 33.2 years (± 12.5 years). All the scores for each INQoL domain (weakness, fatigue, activities, independence, social relationship, emotions, body images) and the derived QoL total score, significantly improved during the observation period, except the muscle locking and pain items. Changes in emotions and social relationships were more relevant in females compared to males. Social relationships were affected also by a longer disease duration (> 30 years). In SMA3 non-walker patients, activities ameliorate better compared to walkers.

In our cohort, adult SMA patients showed a global improvement at the INQoL assessment over 14 months of nusinersen treatment. QoL assessment is relevant to SMA multidisciplinary evaluation.

Exploring face mobility in SMA

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Background. Patients involved in the Expanded Access Program experience with nusinersen in spinal muscular atrophy (SMA) reported variable degrees of changes in the oro-facial district with treatment, but there are no data about facial mobility and general consensus for testing it.

Aims. to investigate new quantitative non-invasive measures of facial mobility in SMA.

Methods. We assessed facial mobility through an easy-to-interpret index based on a face tracking algorithm that exploits Facial Action Coding System (FACS) in patients with SMA at rest and while performing 7 specific tasks: frowning, eye closure without exertion, eye closure with exertion, tight-lipped smile, smile, kiss, cheeks inflation. Based on the FACS encoding system, a set of 56 facial landmarks was defined and tracked in the 2D image space per each expression, using a self-developed software

(TrackOnField, BBSof S.r.l.). These landmarks defined 40 distances that were normalized to the corresponding quantities of the neutral expression. Then, a face mobility index (FMI) was calculated per each subject task.

Results. 62 patients were recruited: 28 females, 34 males; 8 pts SMA1, 26 SMA2, 27 SMA3, 1 SMA4; mean age 27.16 (\pm 18.62) years old. Preliminary data from 34 patients showed that the task involving a greater FMI was smile (17.97), followed by eye closure with exertion (15.96) as expected.

Conclusions. Our preliminary data suggest that this may be a potential measure to track possible alterations on facial muscles' mobility associated to the disease and to investigate the impact of treatments aiming at improving facial mobility.

Dysregulation of lncRNAs and mRNA targets during skeletal muscle development in a patient-derived induced pluripotent stem cell (iPSC) model of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive cortical, bulbar and spinal, motor neuron (MN) death, leading to muscle wasting. Although it is generally accepted that ALS is primarily due to MN degeneration, upcoming evidences show an early involvement of skeletal muscles too. Different causative genes associated to ALS are involved in RNA metabolism; among non-coding RNAs, long-non coding RNAs (lncRNAs) are emerging as molecular contributors to ALS pathophysiology because of their role in regulating gene expression.

Here, we analyzed the expression levels of HOTTIP, MALAT1 and NEAT1 lncRNAs, known to be involved in the development and homeostasis of the skeletal muscle, in a human induced pluripotent stem cell (hiPSC) model differentiated towards a myogenic destiny through a small molecule-based protocol, obtained from ALS patients and healthy controls. The expression of key markers of skeletal muscle development was analyzed by qPCR. Further,

mRNA targets for the lncRNAs were predicted *in silico*, and validated by qPCR.

We reported a differential lncRNA and mRNA target expression pattern in ALS-mutant cell lines compared to controls, particularly at the mesodermal progenitor, early myocyte and myotube stages. Specifically, through hierarchical clustering analysis we identified specific clusters of lncRNAs/mRNA targets characterizing ALS cell lines, suggesting that an altered expression of these molecules might contribute to the disease pathogenesis.

These data highlight the role of HOTTIP, MALAT1 and NEAT1 as potential important players in muscle dysregulation in ALS. Thus, they could represent possible targets for new therapeutic strategies.

6MWT as measure of fatigability in sma type 3 patients treated with nusinersen

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Spinal muscular atrophy (SMA) is an autosomal-recessive motor neuron disease causing progressive muscular atrophy and weakness. Nusinersen, an antisense oligonucleotide able to increase functional SMN protein modifying the SMN2 pre-mRNA splicing, is proven to significantly modify the natural course SMA type 1 in infants and provides benefit even in adult SMA patients. Since fatigue represents an additional dimension of impaired motor function in SMA type 3 patients, hence we aimed to investigate the impact of nusinersen on fatigability (an objective measure of fatigue) through the 6-minute-walking-test (6MWT) in SMA type 3 patients. From a large Italian cohort of patients, we selected 58 ambulant adult SMA type 3 patients being treated with nusinersen and we analyzed data on 6MWT from baseline (T0, beginning of treatment) to 14 months of treatment (T14). Mean age at baseline was 39.6 ± 16 years. No significant reduction in the meters walked from minute 1 to minute 6 was found at T0 (60.6 ± 20.9 vs 56.38 ± 27 m) and T14 (64.0 ± 19.0 vs 54.16 ± 22.8 m). The analysis of variance for repeated measures for the distance walked at every single minute of the 6MWT during follow-up did not show statistically significant differences. Moreover, we found an average trend of improvement of the total 6MWT over a period of 14-month treatment (329.2 ± 129 vs 310.3 ± 136.3 m). In conclusion, although no relevant fatigability was found in our cohort at baseline and no effect of nusinersen on fatigability through the follow-up period, our data broaden the knowledge of nusinersen effect in adult ambulant SMA patients.

Insights for the development of a miRNA-based therapeutic strategy in ALS exploiting iPSC-derived motor neurons and exosomes

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Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disorder characterized by a progressive degeneration of motor neurons (MNs). A dysregulation of microRNA (miRNA) expression in ALS has been already described, although downstream pathological events associated with MN degeneration have not been clarified yet. miRNAs are highly expressed in central nervous system thus they may play important roles in the etiology or progression of neurodegenerative diseases. In this study, we aimed at investigating whether alteration of miRNAs expression patterns in ALS-MNs may represent a common molecular feature among the different forms of the disease. We performed differential expression profile analysis of miRNAs isolated from ALS-MN and healthy subjects and we identified a small group of downregulated miRNAs in ALS-MNs. Interestingly, a dysregulation of the same subset of miRNAs has been detected in exosomes released from the same ALS-MN cultures. Since bioinformatic analysis showed that these miRNAs regulate several pathways related to MN degeneration, we investigated their potential as disease biomarkers assessing their expression level in cerebrospinal fluid (CSF) of ALS patients. We confirmed a dysregulation of these miRNAs in CSF suggesting their potential clinical relevance. Taken together our results demonstrate that the neurodegenerative phenotype in ALS can be associated with a dysregulation of miRNAs involved in the control of disease-relevant molecular pathways. The possibility of tuning entire gene networks with a specific subset of miRNAs may provide significant insights on the development of effective new miRNA-based therapies and could be useful as disease biomarkers.

Neurofilament light chain and Profilin-1 in adult SMA patients under nusinersen treatment: 26-months follow-up

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As an update of our study in 30 adult SMA type 3 patients we tested as potential biomarkers Neurofilament light chain (NfL) and Profilin-1 (PFN-1) during a 26 months follow-up (timepoint M6).

PFN-1 is a small actin-binding protein required in both the presynaptic and the postsynaptic compartment with a role in regulating cytoskeletal architecture and dynamics of neurons (Witke, 2004).

CSF NfL was tested with an enzyme-linked immunosorbent assay (ELISA) kit (UmanDiagnostics, Sweden). PFN-1 was measured with a commercial manual ELISA kit (Cusabio, China) in CSF samples of 6 patients (3 sitters 3 walkers) at time points L1, L3 and M2 and in every available serum sample from time point L1 to time point M6; 19 serum samples of healthy donors as a control group.

Mean NfL at M6 was 381.83 ± 455.71 ng/L, slightly higher than baseline but not significantly different from M3.

PFN-1 concentration in all 18 CSF samples was below the lower limit of quantification (< 31.25 ng/L). Serum PFN-1 at baseline was higher in SMA group than in healthy controls (mean 1016 vs 608 ng/L, $p = 0.001$ Student's t test). PFN-1 showed a complex dynamic during loading phase, with a significant reduction at L4 compared to baseline. No correlation was found with NfL and motor scores at each time point.

PFN-1 as an exploratory cytoskeletal biomarker changed significantly during the first two months of treatment. To our knowledge this is the first report of PFN-1 determination in serum of SMA patients.

Parental mosaicism in aars1-related hereditary neuropathy

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Hereditary neuropathies represent the most common inherited neurological conditions and show wide clinical and genetic heterogeneity. To date, more than 100 genes have been described to cause Charcot Marie Tooth Disease (CMT) and the related disorders, as distal hereditary motor neuropathy (dHMN) and hereditary sensory neuropathy (HSN).

Next generation sequencing (NGS) has speeded up the diagnosis of hereditary diseases and customized tar-

geted NGS panels of disease relevant genes have been developed and used in clinical practice.

We describe a 45 years old patient with distal lower limb predominant sensorimotor neuropathy clinically manifested from the age of 30 and characterized by axonal disfunction with associated demyelination.

NGS custom panel analysis of 77 genes associated with CMT and related conditions was performed with an Illumina custom Nextera Rapid Capture panel and sequencing on Illumina MiSeq. The analysis revealed in the AARS1 gene (OMIM * 601065) the c.986 G > A (p.Arg329His) heterozygous missense variation, a known and recurrent mutation described worldwide.

Segregation analysis through Sanger sequencing in the healthy parents showed the absence of the variation in the father and an ambiguous nucleotide annotation by Sanger in the mother. Indeed the NGS analysis demonstrated in the mother DNA a clear mosaicism for the variant.

NGS analysis is very sensitive in detecting mosaicsms, which should be always analysed by family segregation in order to identify the heterozygous parent and to define the risk or recurrence in the family.

Quantitative MRI evaluation of muscle involvement of lower limbs in amyotrophic lateral sclerosis (ALS): a pilot longitudinal study

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Biomarkers of disease progression and outcome measures still lack for ALS. Muscle MRI can play a role to track longitudinal changes and to predict response to treatment in clinical trials.

We applied quantitative muscle MRI to evaluate disease progression and explore any clinical correlation in ALS.

A cohort of newly-diagnosed ALS patients, longitudinally scored using the leg subscores of ALS Functional Rating Scale Revised (ALSFRS_r), was enrolled. The muscle MRI protocol (6-point Dixon GRE and multi-echo TSE T2w) was implemented for quantification of fat fraction (FF) and water T2 (wT2). Twelve thigh muscles six leg muscles were manually drawn for each side. Eleven age-matched healthy controls were enrolled for comparison.

Fifteen patients (M/F 8/7; average age 62.2, range 29-79) diagnosed with possible (n = 2), probable (12) or definite (1) ALS were enrolled (11 spinal onset, 4 initial bulbar involvement). All patients performed muscle MRI at T0, nine at T1 (6 mo), and seven at T2 (12 mo). At baseline wT2 was significantly elevated in ALS subjects compared to controls for several thigh and mainly for leg muscles; FF was only elevated in a few thigh muscles. wT2 decreased over time in line with worsening in the leg subscores of ALSFRS_r (mainly at the leg level and in the anterior and medial compartment of the thigh); FF increased significantly in the leg muscles over time (mainly in the triceps surae).

In ALS quantitative muscle MRI represents a non-invasive tool capable of describing the trajectory of pathogenic modifications in the muscle.

Use of 3D printer in a rehab lab for the creation of customized assistive devices with users with radiation-induced brachial plexopathy to increase participation: case study

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Background. Villa Rosa RehabLab, Trento Italy, aims to design 3D printed personalized Assistive Devices (AD) to facilitate and promote participation through a user-centred co-design process.; direct involvement of the user in the design process ensures a correspondence of the AD to his/her needs, aiming to empower the person in the therapeutic strategy, ensuring the AD's continuous use and avoiding stigmatization. The use of 3D printer is increasingly popular in the medical world, particularly in rehabilitation and occupational therapy for the manufacture of personalized adaptations and assistive devices.

M.A. 58 y.o., diagnosed with radiation-induced brachial plexopathy since 2012, at the initial occupational therapy interview reported difficulty in cutting hard foods, reporting pain when he presses the knife with his left arm. Patient's quality of performance was observed and self-perception of performance and satisfaction

scored using the Canadian Occupational Performance Measure (COPM).

Objective. Improve quality of performance and decrease pain when performing this task.

Methods. After ascertaining that no commercial AD was available, an AD dedicated to this function was designed by the user on paper, and afterwards the occupational therapist created a wood prototype. Once the functionality of the prototype was ascertained, the user, guided by the therapist, drew the object with desired shape and sizes using FUSION360, which was then fabricated with the 3D printer.

Result. The client's quality of performance improved using the fabricated AD, as did his COPM scores.

Conclusions. The RehabLab and use of 3D printer can improve independence and participation with individuals with radiation-induced brachial plexopathy.

Cell-penetrating peptides-conjugated Morpholino: a novel therapeutic approach for the treatment of spinal muscular atrophy symptomatic cases

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Spinal muscular atrophy (SMA) is a motor neuron disease and the first known genetic cause of infant mortality. Recently approved therapies have shown efficient results only if administered during the pre-symptomatic phase, that seldom corresponds to the period when the disease is diagnosed in patients. Therefore, the issue of a symptomatic-suitable treatment, efficient across different clinical phenotypes, is strongly present in a clinical perspective.

We have already demonstrated that the ASO variant Morpholino (MO) is able to increase the production of a functional SMN protein and rescue the murine phenotype in pre-symptomatic phase, after intracerebroventricular administration. However, this treatment resulted almost ineffective if administered during the symptomatic phase. The conjugation with Cell-Penetrating Peptides (CPPs) may represent a promising therapeutic strategy to address this issue, allowing the MO to overcome the blood-brain barrier by a systemic administration thus expanding the therapeutic window.

We investigated the efficacy of CPPs in delivering MO to the central nervous system in symptomatic mice

through an intraperitoneal injection, demonstrating that the conjugation with r6 peptide can improve MO biodistribution and increase SMN levels, rescuing the pathological phenotype. Histological examination on SMA treated mice showed a significant increase in the number of motor neurons and innervation of neuromuscular junctions. These data were supported by a striking increase in survival and motor functions, confirming the safety and efficacy of this approach which has never been observed with other compounds in a symptomatic phase of the disease, laying the ground for the development of future clinical trials for SMA.

Oro-facial and bulbar involvement in SMA (OBI-SMA): outcome measures & end-point assessments

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Background. While there is general consensus on the motor function scales to be used in muscle strength and functional assessment, little is available for testing of oro-facial muscles and function, yet the pre-swallowing phase of feeding is affected not only in SMA1, but also in the other types of SMA.

Aims. To investigate strength and function of the oro-facial and brainstem muscles in a cohort of SMA patients treated with nusinersen and in a cohort of naive patients.

Methods: This is a 20-months observational, multi-center parallel study involving 120 patients with all types of SMA either on treatment or not subjected to lip and tongue strength assessments, swallowing and mastication functional tests and clinical nutritional assessments.

Results. 140 patients have been enrolled to date. 65% are on treatment while 35% are not (48% SMA2, 31% SMA3, 21% SMA1). 95% of SMA1, 50% of SMA2 and 27% of SMA3 are underweight. 17% of SMA2 and 33% of SMA3 are overweight. IOPI lip and tongue strength (KPa) and mouth opening (cm) was 2.6 and 2 KPa and 2.5 cm for SMA1; 12.9 and 16.2 KPa and 2.6 cm for SMA2; 19 and 42.5 KPa and 4.2 cm for SMA3. SMAHI subscores referring to swallowing and bulbar functions correlated to the nutritional and swallowing abilities of the patients including PEG tubes.

Conclusions. Our preliminary data suggest that IOPI and SMA-HI swallowing and bulbar subscores may be

potential tools to track possible changes on orofacial and orobulbar functions related to the disease itself or to treatment.

The experience with nusinersen (Spinraza) in pediatric SMA patients in Emilia-Romagna in a regional network

Scarpini G.¹, Giannotta M.¹, Not R.¹, Capelli P.¹, Testoni C.², Pisani F.³, Piccolo B.³, Fusco C.⁴, Frattini D.⁴, Vergine G.⁵, Farina M.⁶, Sarajlia J.⁷, Marchetti F.⁸, Piccinini G.⁸, Pini A.¹

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Nusinersen (Spinraza) is the first drug approved in Italy in 2017 for the treatment of SMA patients. Since its approval, the drug has been administered in several authorized Italian Centers. In the Emilia-Romagna (ER) region we started to treat SMA patients in 3 Centers authorized to prescribe and administer the drug (Bologna, Reggio-Emilia, Parma), and in 2 Centers authorized for administration (Ravenna and Rimini) in collaboration with the Bologna Centre. After the consent of the Ethics Committee we collected data regarding type of SMA, age of onset and of diagnosis in a cohort of 26 patients treated with Spinraza, in order to study a possible correlation between these variables and the response to treatment. Moreover, procedural aspects were considered: type of hospitalization, type of anesthesia and management of the post-procedural phase. The response to therapy has been periodically measured by clinical evaluations with motor function scales and systematic collection of quality of life improvements. Instrumental investigations (muscle MRI and CMAP evaluation) were performed in collaborating patients before the start of treatment and again during the follow up. Light chain neurofilaments (NFL) levels were also studied in 17 patients.

The creation of a regional network among all the Centers made it possible to share the same operative procedure for the treatment with Spinraza, to get real world data on all treated patients and to reduce the burden for the families related to the procedure and to the travel, allowing patients to be treated close to home.

AUTHOR INDEX

A

Abel F., 37
 Agosto C., 31
 Aimo A., 57
 Ajdinaj P., 50, 51
 Albamonte E., 29, 32, 65
 Alfano L.N., 33
 Aliverti A., 38
 Altamura C., 52
 Amatetti M., 51
 Amerio P., 44
 Andreassi G., 51
 Angelini C., 43, 55
 Angelucci D., 51
 Antognozzi S., 45
 Antonaci L., 29
 Antonini F., 42
 Antozzi C., 40
 Aquaro G.D., 57
 Aringhieri G., 34
 Arrigoni F., 47
 Assini A., 55
 Astrea G., 36, 38

B

Baggi F., 40
 Baldelli E., 56
 Baldinotti F., 57, 59
 Ballante E., 63
 Bandini F., 55
 Baranello G., 30
 Baratto S., 42, 53
 Barbone F., 51
 Bardelli D., 61
 Barison A., 57
 Barp A., 56
 Bartolini M., 59
 Battini R., 36, 38
 Bax C., 41
 Becchiati S., 56, 60
 Bello L., 30, 34, 37, 51, 60, 61, 62
 Benedetti L., 55
 Benini F., 31
 Berardinelli A., 30, 37, 59, 61
 Bergsland N., 63
 Beronio A., 55
 Bersani M., 64
 Bertini E., 29, 32
 Bettica P.U., 50

Bianchi F., 35
 Biella F., 62
 Blaschek A., 33
 Blasevich F., 35, 57
 Boffa L., 53
 Bonanno S., 29, 30, 35, 39, 40, 57, 58, 60, 61
 Bönnemann C.G., 33
 Bonzi G., 32
 Bortolani S., 30, 60, 61
 Bossolasco P., 61
 Bozzoni V., 30, 60-62
 Bragato C., 35, 57
 Bresolin N., 45, 49, 64
 Brighina F., 39, 54
 Brolatti N., 29, 36
 Brugnoli R., 52
 Brunetti-Pierri N., 43
 Bruno C., 29, 30, 36, 37, 42, 45, 48, 53
 Brusa C., 35, 37
 Brusa R., 35, 47
 Bruzzone S., 42
 Buchignani B., 36, 38

C

Cabona C., 55
 Caligo M.A., 59
 Caltagirone C., 41
 Campana C., 53
 Campanale C., 52
 Canavese C., 52
 Canioni E., 37, 52
 Capelli P., 65
 Caponnetto C., 30, 61
 Caputo V., 41
 Caria F., 56
 Carraro E., 60, 65
 Carratù M.R., 52
 Casagrande S., 64
 Casalini E., 36
 Cascella R., 41
 Casiraghi J., 56
 Cassandrini D., 36, 38
 Cataldi M., 53
 Cateruccia M., 35
 Cattaneo C., 65
 Catteruccia M., 29, 37
 Caumo L., 30, 60, 61, 62
 Cavallina I., 47
 Cazzaniga S., 50

Cella A., 55
 Cerri F., 30, 61
 Cesaroni E., 32
 Cestarollo M., 34, 51
 Chan E., 37
 Chesshyre M., 37
 Chico L., 59
 Church K., 33
 Cibin F., 60
 Ciceri T., 47
 Cinnante C.M., 44, 50
 Ciscato P., 2, 43-45, 49
 Coccia M., 30, 60, 61
 Colantoni L., 41
 Colombo P., 59
 Comi G.P., 30, 32, 37, 40, 44, 45, 49, 50, 61, 62, 64
 Conte I., 42
 Conte R., 34
 Coratti G., 29, 65
 Corti S., 32, 44, 45, 49, 61, 62, 64
 Cosma C., 62
 Costa A., 44
 Cotti Piccinelli S., 32, 35, 48, 56
 Crippa A., 47
 Cristillo V., 32

D

D'Alessandro, 47
 D'Ambrosio P., 35, 40, 47, 53, 54
 D'Amico A., 29, 32, 37
 D'Angelo M.G., 37, 38, 47, 59
 D'Apice M.R., 59
 Darras B.T., 30
 de Groot H., 37
 Dekdebrun J., 56
 Deligianni X., 63
 Delle Fave M., 38
 Del Sette M., 55
 De Lucia S., 29
 Del Vecchio Blanco F., 40, 43, 49, 51
 Del Zotto G., 42
 De Mattia E., 56
 De Rosa M.A., 51
 D'Errico E., 30, 61
 Desaphy J.-F., 52
 Diamanti L., 63
 Di Bari A., 37, 56, 65
 DiDuca M., 53
 Diella E., 38
 Di Iorgi N., 36
 Di Muzio A., 39, 50, 51
 Diodado D., 35
 Di Stefano V., 39, 54

Dodman A., 30
 Donati M.A., 36
 Dowling J.J., 33

E

Eichinger K., 56
 El-Khairi M., 30
 Emdin M., 57
 Eoli M., 52

F

Fabris M., 63
 Falcier E., 56
 Falzarano M.S., 48
 Falzone Y., 59
 Farina M., 65
 Farinato A., 52
 Fenu S., 35
 Ferlini A., 35, 48, 63
 Ferrari-Aggradi C.R., 56
 Ferraro M., 30, 60
 Ferri L., 39, 50, 51
 Fierro B., 54
 Figini S., 63
 Filosto M., 30, 32, 35, 36, 48, 52, 56, 61
 Fiorillo C., 45, 48, 53
 Foley A.R., 33
 Foppoli L., 63
 Fortunato F., 35, 48, 49, 63
 Frangiamore R., 40
 Frattini D., 65
 Frezza E., 53
 Frisoni M.C., 56, 60
 Frosini S., 38
 Fusco C., 65
 Fusto A., 37

G

Gadaleta G., 30, 35, 47, 61
 Gagliardi D., 62
 Gagliardo A., 39, 54
 Gallone A., 37, 39, 40, 57, 58
 Gallone S., 36
 Galvagni A., 48
 Garbellini M., 43, 64
 Gardani A., 30
 Garibaldi M., 39
 Gasperini B., 64
 Gatti V., 56
 Gazzerri E., 42
 Gerber M., 30
 Gerevini S., 49

Gessi M., 48
 Giacobbe A., 45
 Giagnorio E., 61
 Giannini F., 35, 36
 Giannoni A., 57
 Giannotta M., 45, 65
 Giardina E., 41
 Giossi R., 29
 Giubergia A., 47
 Goglia M., 53
 Gorni K., 30
 Govoni A., 30, 32, 61
 Grandis M., 30, 55, 61
 Greco G., 53
 Griffin D.A., 33
 Grigoratos C., 57
 Grisanti S.G., 30, 55
 Gualandi F., 63

H

Hackman P., 34
 Hogrel J.-Y., 37

I

Iacono S., 39, 54
 Ianes P.G., 64
 Iammarino M.A., 33
 Iannibelli E., 57
 Ingenito G., 29
 Iossa F., 56
 Italiano C., 56

J

Janez Z., 44
 Johari M., 34
 Johnson N., 56

K

Kletzl H., 30
 Koenig E., 33
 Kuntz N., 33

L

Labella B., 44
 Lai E., 41
 Lampis V., 47
 Lanza P., 39
 Lanzi G., 48
 Lauria G., 52, 61
 Lawlor M.W., 33
 Leali M., 57

Lehman K.J., 33
 Leone D., 29, 37
 Lewis S., 33
 Liguori R., 30, 60, 61
 Linari M., 42
 Li X., 33
 Lizio A., 56
 LoMauro A., 38
 Lopercolo D., 36
 Lops J., 65
 Lowes L.P., 33
 Lu, 39
 Lucchiari S., 43
 Lupica A., 54
 Lupone S., 56
 Luque H., 34

M

Maggi L., 29, 30, 35, 37, 39, 40, 49, 52, 57, 58, 60, 61
 Maghnie M., 36
 Magoni M., 44
 Magri F., 36, 37, 40, 43, 44, 45, 49, 50
 Maioli M.A., 30, 36, 61
 Malacarne C., 61
 Malandrini A., 35, 36
 Mandich P., 36
 Mani E., 47
 Manini A., 44
 Mantegazza R., 30, 35, 40, 52, 57, 61
 Mantegazza R.E., 60
 Manzur A., 37
 Marchetti F., 65
 Marchi E., 38
 Marcuzzo S., 61
 Maresk K., 37
 Margutti A., 63
 Mari F., 32, 36
 Marija M., 44
 Marinella G., 36, 38
 Marrosu G., 30, 61
 Mascheretti S., 47
 Masrori P., 62
 Massa R., 36, 53
 Masson R., 30
 Mastellaro S., 51
 Matà S., 59
 Mauro L., 56, 65
 Mazurkiewicz-Beldzi ska M., 30
 Mazzola M., 32
 Meadows A.S., 33
 Melzi V., 62
 Mendell J.R., 33
 Meneri M., 30, 61, 62

Mercante A., 31
 Mercuri E., 29, 65
 Merico E., 32
 Merlo B., 37
 Messina S., 29, 32, 37, 53
 Mietto M., 48
 Milani D., 45
 Miller W., 33
 Minetti C., 36, 42, 45, 53
 Missaglia S., 55
 Moggio M., 40, 44, 45, 49
 Molteni M., 59
 Monastra F.M., 35
 Mongini T.E., 30, 36, 37, 47, 60, 61
 Montanaro F., 48
 Montrasio S., 50
 Mora M., 57
 Morgan J., 48
 Müller-Felber W., 33
 Munot P., 37
 Muntoni F., 37, 48
 Musacchia F., 40
 Musarò A., 50
 Musso G., 62
 Musumeci S.A., 54
 Muzic S.I., 63

N

Napoli L., 45
 Napoli M.M., 51
 Narciso E., 55
 Neri M., 63
 Nesti C., 59
 Neuhaus S., 33
 Nicocia G., 30, 35, 40, 53, 54
 Nigro V., 37, 40, 42, 43, 47, 49, 51, 58
 Niks E.H., 37, 50
 Nizzardo M., 32, 62, 64
 Nobile M., 47, 59
 Not R., 65
 Noursalehi M., 33
 Nuredini A., 32

O

Onore M.E., 40, 49, 51
 Ostrowska I., 32

P

Padovani A., 32, 44, 48, 56
 Pagliari E., 64
 Palazzo G., 65
 Palladino A., 58

Pane M., 29, 37, 65
 Panicucci C., 36, 37, 42, 45, 53
 Paoletti M., 63
 Parravicini S., 37
 Pasanisi B., 58
 Pascuzzo R., 38
 Passamano L., 30, 47, 49, 58, 61
 Passino C., 57
 Pavesi G., 30, 61
 Pedemonte M., 36, 45, 53
 Peduto C., 35
 Pegolo E., 60
 Pegoraro E., 30, 34-36, 37, 51, 60-62
 Pera M.C., 29, 65
 Peric S., 29
 Perilongo G., 31
 Peruzzo D., 47
 Pezzini D., 44
 Picaro L., 33
 Piccinini G., 65
 Piccolo B., 65
 Pichiechio A., 63
 Picillo E., 37, 47, 49, 51, 58
 Pignolo A., 54
 Pilla F., 64
 Pilotto A., 32
 Piluso G., 40, 43, 51
 Pini A., 45, 52, 658
 Pintus S., 42
 Piontek M., 32
 Piras R., 29, 30
 Pirola A., 56, 65
 Pisani F., 65
 Pistininzi C., 38
 Plebani M., 62
 Poggetti F., 40
 Poli L., 44
 Politano L., 30, 37, 49, 58, 61
 Porcelli V., 29
 Porfiri L., 32
 Powers B., 33
 Pozsgai E.R., 33
 Prada V., 55
 Prasad S., 33
 Previtali S.C., 30, 58, 59, 61
 Primiano G., 35
 Principi E., 42
 Pugliese A., 35, 39, 40, 53, 54

Q

Quartana M., 54
 Quinlivan R., 37

R

Raffaghello L., 42
 Ramos J.A.F., 32
 Ranieri M., 41
 Ratti A., 61
 Reash N.F., 33
 Refran J., 56
 Ricci E., 41
 Ricci F., 36, 47, 58
 Ricci G., 30, 34, 36, 41, 57, 59, 61
 Rico S., 33
 Ricotti V., 37
 Ridout D., 37
 Riguzzi P., 34, 51
 Riley M., 37
 Rimessi P., 63
 Ripolone M., 40, 50
 Risi B., 30, 32, 48, 56
 Rispoli M.G., 39, 50, 51
 Rizzuti M., 62, 64
 Robb S., 37
 Rodino-Klapac L.R., 33
 Rodolico C., 36, 39, 40, 53, 54
 Rolle E., 47
 Romani C., 48
 Romano F., 51
 Ronchi D., 43, 44, 45, 49
 Rose K., 30
 Rossi F., 47
 Rossi R., 48
 Rossi T., 52
 Rubegni A., 34, 36, 38
 Ruggieri A., 57
 Russo A., 38, 47, 59

S

Saade D.N., 33
 Sabbatini D., 37
 Saccani E., 30, 61
 Saccomanno D., 64
 Salamon E., 31
 Salani S., 43, 49
 Salmin F., 29, 60, 65
 Salvi E., 61
 Sancricca C., 35
 Sansone F., 34
 Sansone V.A., 29, 32, 37, 56, 60, 65
 Santini A., 31
 Santini S., 63
 Santorelli F.M., 34, 36, 38, 59
 Sarajlia J., 65
 Sarkozy A., 37

Savarese M., 34, 58
 Sawacha Z., 60
 Scala M., 45, 53
 Scalco R.S., 30
 Scarpini G., 65
 Scarsi E., 55
 Schenone A., 30, 55, 61
 Schiano di Cola F., 32
 Schirinzi E., 32, 41
 Sciacco M., 35, 40, 43, 45, 49, 50
 Scudieri P., 42
 Scutifero M., 58
 Scuvera G., 45
 Seferian A.M., 33
 Selicorni A., 49
 Selvatici R., 48, 63
 Servais L., 33, 37
 Sette E., 63
 Sframeli M., 29, 32
 Shieh P.B., 33
 Siciliano G., 30, 32, 34-36, 52, 57, 59, 61
 Silani V., 35
 Silvestrini M., 30, 60, 61
 Simone I.L., 30, 61
 Solazzo F., 63
 Solero L., 35
 Solve-RD DITF-EuroNMD, 43
 Sorarù G., 30, 37, 60, 61, 62
 Sperti M., 59
 Spiro Santovito L., 58
 Stevic Z., 29
 Strafella C., 41
 Straub V., 37
 St Romain J., 56

T

Taiana M., 32
 Tanel R., 30, 60, 61
 Tarabelloni A., 59
 Tasca G., 41
 Tavian D., 55
 Tesei A., 59
 Testoni C., 65
 Thornton C., 56
 Ticci C., 36
 Ticozzi N., 35
 Tiziano D., 32
 Tizzoni F., 59
 Todiere G., 57
 Tonacci A., 34
 Tonin P., 36, 52
 Torella A., 40, 43, 47, 49, 51, 58
 Torre E., 55

Torri F., 34, 57, 59
 Toscano A., 53, 54
 Trabanelli C., 63
 Tramacere I., 30, 58, 60, 61
 Travaglioni L., 37
 Traverso M., 45, 48, 53
 Trojsi F., 30, 61
 Trucco F., 37
 TTN-RNaseq Working Group, 34
 TUDP, 49
 Tugnoli V., 63
 Turri M., 30, 60, 61

U

Udd B., 34, 42
 Urbano, G. 47

V

Vacchiano V., 30, 60, 61
 Valentino M.L., 45
 Van Damme P., 62
 Vantini S., 38
 Varavallo A., 43
 Velardo D., 44, 45, 50
 Vergaro G., 57

Vergine G., 65
 Verriello L., 30, 61
 Vianello S., 37
 Vihola A., 34
 Villa F.M., 34, 47, 51
 Vita G.L., 32
 Vlodavets D., 30

W

Wallis C., 37
 Wischmeijer A., 43

X

Xiong H., 30

Z

Zangaro V., 34, 51
 Zanin R., 29, 30, 58, 60, 61
 Zanolio M., 40, 49, 51
 Zanolini A., 29, 56, 65
 Zanolini E., 30
 Zanolini S., 40, 43, 49, 50
 Zara F., 45, 53
 Zeuli R. 43, 49, 51
 Zuccarino R., 64

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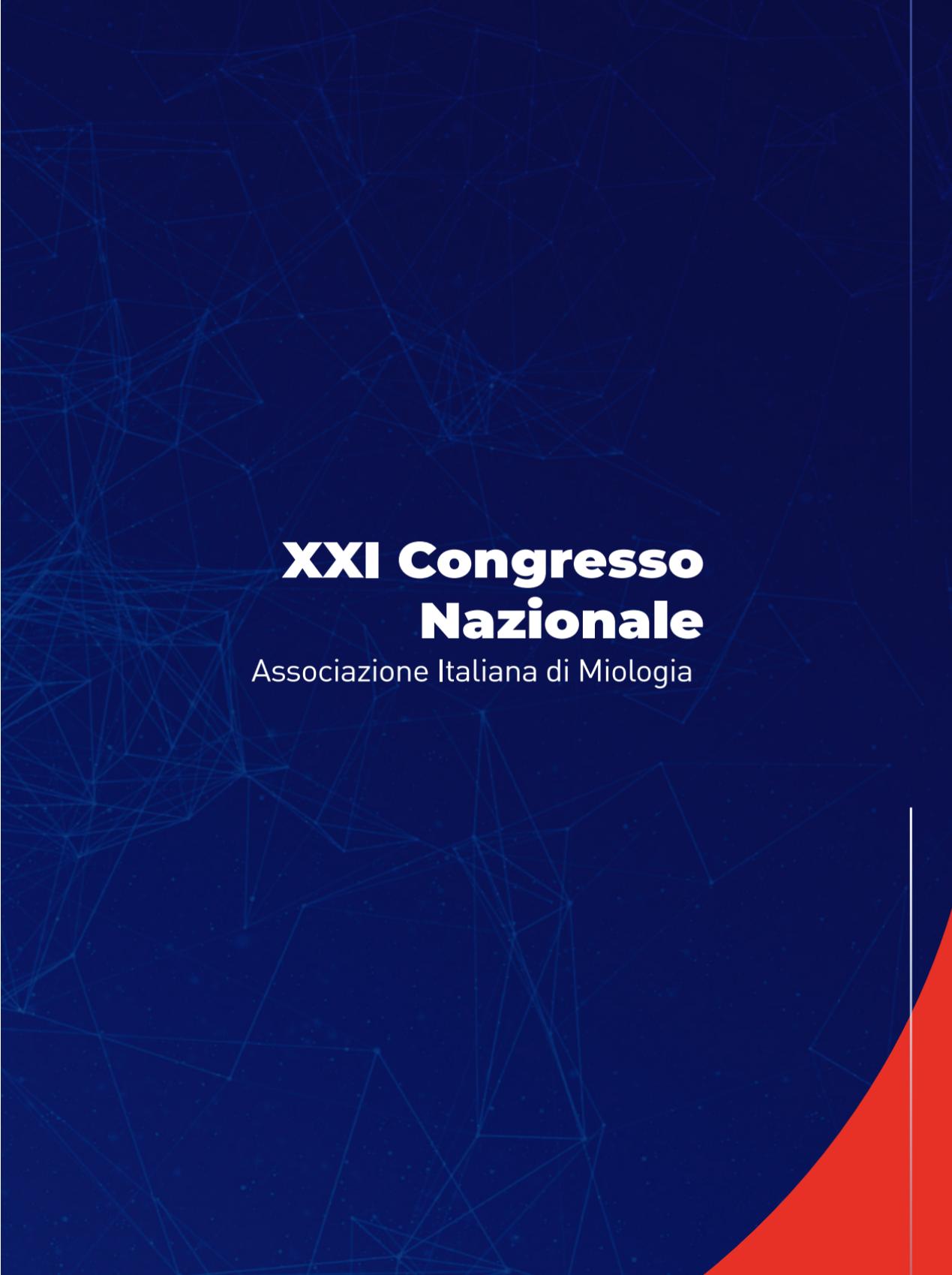


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