

ACTAMYOL

Vol. XLV - MARCH 2026 (SUPPL. 1)

THREE-MONTHLY

Official Journal of

**MEDITERRANEAN SOCIETY OF MYOLOGY
and ASSOCIAZIONE ITALIANA DI MIOLOGIA**

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Giovanni NIGRO and Lucia Ines COMI

ACTA **MYOLOGICA**

(Myopathies, Cardiomyopathies and Neuromyopathies)

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Dept. of Experimental Medicine, University of Campania "L. Vanvitelli"
Piazza Miraglia - 80138 Naples, IT
Tel. +39 081 5665300 - Fax +39 081 5665101
actamyologica2@gmail.com
luisa.politano@unicampania.it

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All correspondence should be addressed to:

Mediterranean Society of Myology - Cardiology and Medical Genetics - Primo Policlinico - Piazza Miraglia - 80138 Naples, Italy - Tel. +39 081 566 5300 - Fax +39 081 566 5101.

Luisa Politano, via Ferrarecche 57, 81100 Caserta, Italy; email: actamyologica2@gmail.com

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XVI RIUNIONE ANNUALE
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PER LO STUDIO DEL
SISTEMA NERVOSO PERIFERICO
ASNP



Associazione Italiana
Sistema Nervoso Periferico



BOLOGNA

Palazzo dei Congressi

13 - 16
maggio
2026

**PRELIMINARY
PROGRAM**



con il patrocinio di



XXVI NATIONAL CONGRESS OF ITALIAN ASSOCIATION OF MYOLOGY

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Wednesday, May 13th, 2026

••• PARALELL ROOM ITALIA

PRE-CONGRESS COURSE - NO CME

11.30 - 14.00 **Pre-congress course | NO CME**
Chairs: *Maurizio Moggio, Lucio Santoro*

**Distal Amyotrophy: a cross-sectional
clinical presentation
in neuromuscular disorders**

Distal neuropathic amyotrophy
Stefano Previtali

Distal myopathic amyotrophy
Marina Grandis

Diagnostic tools in differential diagnosis: pathology
Daniele Velardo

Diagnostic tools in differential diagnosis: neurophysiology
Stefano Tozza

Diagnostic tools in differential diagnosis: imaging
Giorgio Tasca

CONGRESSO AIM ETS/ASNP 2026

RATIONALE

The organization of a joint congress between the Associazione Italiana di Miologia (AIM) and the Associazione per lo Studio del Sistema Nervoso Periferico (ASNP) arises from the increasingly urgent need to address neuromuscular disorders in an integrated manner, in light of therapeutic and diagnostic advances that require a translational and multidisciplinary vision.

In 2026, the decision was made to organize this joint congress with the aim of building a scientific bridge between two communities that share research areas, advanced technologies, and clinical challenges. The meeting is intended to represent a crucial opportunity to unite expertise, share scientific evidence, and define new strategies in the field of neuromuscular diseases.

Today, an interdisciplinary approach represents the only effective way to address the biological and clinical complexity of these conditions, promote cutting-edge research, and improve patient care.

The 2026 Bologna Congress aims to establish a scientific connection between the fields of muscle and peripheral nervous system research, bringing together basic and clinical expertise in neuromuscular regeneration, genetic and inflammatory diseases, immune-mediated complications, advanced imaging, artificial intelligence, and novel therapies. Through plenary and parallel sessions, the program will foster dialogue among research groups and specialists from different backgrounds, encouraging the critical sharing of data, updates on ongoing clinical trials, and the development of biomarkers and quantitative tools for diagnosis, stratification, and disease monitoring. The ultimate goal of the congress is to stimulate long-term scientific collaborations between the two communities, promote multicenter studies and joint projects, and contribute to shaping future research directions in neuromuscular diseases, with a truly integrated perspective between muscle and peripheral nerve.



CONGRESSO AIM ETS / ASNP

2026

PROGRAM

Wednesday, May 13th, 2026

13.00 - 14.00 **Opening Registration**

... PLENARY ROOM EUROPA

14.00 - 14.30 **Greetings and introduction**

Rocco Liguori, Fiore Manganelli, Vincenzo Nigro

14.30 - 15.15 **Main Lecture // #**

Chair: *Rocco Liguori*

Multisystem Proteinopathies

Bjarne Udd

15.15 - 16.30 **Parallel Workshop 1 // #**

Chairs: *Claudio Bruno, Gabriele Siciliano*

Muscle Plasticity: from normal to pathological conditions

Cellular and Molecular Mechanisms of Skeletal Muscle Plasticity
in the Era of Omics

Roberto Bottinelli

HMGB1 as a Central Regulator of Skeletal Muscle Homeostasis:
Implications for Disease and Ageing

Emilie Vénéreau

Dissecting the cachexia signature for developing a RNA-based therapy

Marco Sandri

... PARALELL ROOM ITALIA

15.15 - 16.30 **Parallel Workshop 2**

Chairs: *Vincenzo Provitera*

**Small fibers, big challenges: an integrated approach to small fiber
neuropathy from clinical, diagnostic, and pathophysiological perspectives**

Clinical criteria and diagnostic workup

Grazia Devigili

Neuropathic Pain: Correlations with Small Fiber Morphology and Function

Eleonora Galosi

Autonomic dysfunction: a morpho-functional approach

Maria Nolano

Current Therapeutic Options and Future Directions

Vincenzo Donadio

••• PLENARY ROOM EUROPA

16.30 - 18.00 **ORAL COMMUNICATIONS**

Chairs: *Alessandra Ferlini, Federica Ricci*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

16.30 - 16.45 NONSENSE VARIANTS IN BECKER MUSCULAR DYSTROPHY:
CLINICAL COURSE AND DISEASE SEVERITY

Domenico Gorgoglione

16.45 - 17.00 DUCHENNE MUSCULAR DYSTROPHY DRIVES T CELL REMODELING

Chiara Villa

17.00 - 17.15 CHARACTERIZING INITIAL SYMPTOMS AND FUNCTIONAL EVOLUTION
IN BECKER MUSCULAR DYSTROPHY

Angela Petrosino

17.15 - 17.30 EVOLUTION OF SWALLOWING DISTURBANCES IN DUCHENNE
MUSCULAR DYSTROPHY (DMD)

Maria Grazia D'Angelo

17.30 - 17.45 PROSPECTIVE EVALUATION OF SLEEP-DISORDERED BREATHING
AND FUNCTIONAL ASSESSMENT IN DUCHENNE MUSCULAR DYSTROPHY:
DYSTREST STUDY

Marina Pedemonte

17.45 - 18.00 CELL-MEDIATED EXON SKIPPING INDUCES ROBUST DYSTROPHIN
EXPRESSION AT A VERY LATE-STAGE OF DUCHENNE MUSCULAR
DYSTROPHY

Stefano Previtali

••• PARALELL ROOM ITALIA

16.30 - 18.00 **ORAL COMMUNICATIONS**

Chairs: *Mauro Monforte, Maria Lucia Valentino*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

16.30 - 16.45 PROGRESSION DYNAMICS AND DISABILITY MILESTONES
IN CHILDHOOD-ONSET FSHD

Beatrice Ravera

16.45 - 17.00 AN INTEGRATED LONG-READ SEQUENCING WORKFLOW FOR
COMPREHENSIVE MOLECULAR CHARACTERIZATION OF FSHD PATIENTS

Claudia Strafella

Wednesday, May 13th, 2026

- 17.00 - 17.15 INNATE IMMUNE ACTIVATION ASSOCIATED WITH MUSCLE-SPECIFIC FRG1 OVEREXPRESSION
Sebastian Fantini
- 17.15 - 17.30 RETHINKING GENOMICS OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN THE TELOMERE-TO-TELOMERE ERA: PITFALLS IN THE HIDDEN LANDSCAPE OF D4Z4 REPEATS
Valentina Salsi
- 17.30 - 17.45 A TELOMERIC TRANSLOCATION CAUSING FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN A FAMILY WITH NORMAL D4Z4 SIZE
Ilaria Quartesan
- 17.45 - 18.00 UNRAVELING PHENOTYPIC HETEROGENEITY IN FSHD THROUGH MACHINE LEARNING-BASED ANALYSIS OF GENOME VARIANTS
Sara Pini

••• MODULAR PARALLEL ROOM 1-2

- 16.30 - 18.00 **ORAL COMMUNICATIONS // #**
Chairs: *Caterina Garone, Chiara Pisciotta*
- Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion*
- 16.30 - 16.45 HETEROZYGOUS TUBB3 VARIANTS CAUSE ISOLATED OR COMPLEX, AXONAL OR INTERMEDIATE CHARCOT-MARIE-TOOTH DISEASE
Alessandro Bertini
- 16.45 - 17.00 SERUM POLYOLS AS DISEASE BIOMARKERS IN SORD NEUROPATHY
Ilaria Quartesan
- 17.00 - 17.15 A NOVEL 5' UTR CCG EXPANSION IN TBC1D7 CAUSES OCULOPHARYNGODISTAL MYOPATHY
Riccardo Currò
- 17.15 - 17.30 IN VITRO VARIANT SCREENING IMPROVES VARIANT INTERPRETATION IN ACTN2-RELATED MYOPATHIES
Johanna Ranta-aho
- 17.30 - 17.45 GENETIC MODIFIERS IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: A GENOME-WIDE ASSOCIATION STUDY
Elisa Vegezzi
- 17.45 - 18.00 BEYOND DISTAL ARTHROGRYPOSIS: REFINING THE PHENOTYPIC LANDSCAPE OF PIEZO2-RELATED DISORDERS
Giuliana Capece

16.30 - 18.00 **ORAL COMMUNICATIONS**

Chairs: Chiara La Morgia, Paola Tonin

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

16.30 - 16.45 WEARABLE SENSOR-BASED QUANTITATIVE GAIT ANALYSIS
IN METABOLIC MYOPATHIES: A SINGLE-CENTRE EXPERIENCE
Ignazio Giuseppe Arena

16.45 - 17.00 CLINICAL AND GENOTYPIC SPECTRUM OF TWINKLE-RELATED DISORDERS
INSIGHTS FROM A MULTINATIONAL COHORT STUDY
Michelangelo Mancuso

17.00 - 17.15 REAL WORD DATA ON ALGLUCOSIDASE - CIPAGLUCOSIDASE/MIGLUSTAT
SWITCHING IN LOPD: AN ITALIAN MULTICENTER EXPERIENCE
Olimpia Musumeci

17.15 - 17.30 BRAIN PHYSIOLOGICAL TRANSCRIPTOMIC ARCHITECTURE UNDERPINNINGS
OF REGIONAL VULNERABILITY TO STROKE-LIKE LESIONS IN MELAS
Matteo Azzimonti

17.30 - 17.45 SWITCHING FROM ALGLUCOSIDASE ALFA TO AVALGLUCOSIDASE:
REAL-WORLD DATA FROM A SINGLE-CENTER EXPERIENCE
Ignazio Giuseppe Arena

17.45 - 18.00 RITUXIMAB IN IDIOPATHIC INFLAMMATORY MYOPATHIES:
AN ITALIAN MULTICENTER STUDY FROM THE INFLAMMATORY MYOPATHIES
AIM STUDY GROUP
Matteo Lucchini

... PLENARY ROOM EUROPA

18.00 - 18.45 **Symposium sponsored by Santhera | NO CME**
Chair: *Eugenio Maria Mercuri*

**Optimizing Standard of Care Therapy in Duchenne Muscular Dystrophy:
A next generation of steroid with dissociative mechanism**

18.00 - 18.05 Welcome & Introduction
Eugenio Maria Mercuri

18.05 - 18.15 Rethinking Steroid Therapy in DMD: Why Mechanism of Action Matters
Pier Lorenzo Puri

18.15 - 18.25 Looking Beyond the Trial Endpoint: Sustained Efficacy and Long-Term
Functional Preservation in DMD
Luca Bello

Wednesday, May 13th, 2026

18.25 - 18.35 When Treatment Becomes a Risk Factor: Preserving Bone While Treating Muscle in Duchenne

Chiara Panicucci

18.35 - 18.45 Discussion Q&A

Eugenio Maria Mercuri

... PARALELL ROOM ITALIA

18.45 - 19.15 **Lecture sponsored by Novartis | NO CME**

Chair: *Antonella Pini*

Gene therapy in Spinal Muscular Atrophy: goals and expectations

Maria Carmela Pera

19.15 - 19.45 **Lecture sponsored by Alnylam | NO CME**

The Importance of RNAi in the Treatment of hATTR:

The Value of Early Treatment in Patients with Polyneuropathy

Pietro Guaraldi

Clinical Experience with Vutrisiran in Real-World Practice

Stefano Tozza

... PLenary ROOM EUROPA

18.45 - 20.00 ***Myasthenia Gravis**

... MODULAR PARALLEL ROOM 1

18.45 - 20.00 ***CIDP/MMN**

... MODULAR PARALLEL ROOM 2

18.45 - 20.00 ***Mitochondrial Disorders**

*The Study Groups are specialized working groups within the Society, bringing together experts and researchers with a common interest in specific areas of myology and peripheral nerve. These groups focus on advancing knowledge, promoting collaboration, and fostering scientific discussions on various topics related to neuromuscular diseases, muscle biology, and clinical myology.

18.45 - 20.15 **ORAL COMMUNICATIONS**

Chairs: *Emanuele D'Amico, Carlo Minetti*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

18.45 - 19.00 EMERGING ROLE OF MUSCLE-AND FIBROSIS-RELATED MICRORNAS
IN EMERY-DREIFUSS MUSCULAR DYSTROPHIES

Giorgia Farinazzo

19.00 - 19.15 SERUM LIGHT CHAIN NEUROFILAMENTS AS A BIOMARKER
IN VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN PEDIATRIC ACUTE
LYMPHOBLASTIC LEUKEMIA

Giacomo Gotti

19.15 - 19.30 A MULTICENTER STUDY OF CCDC78-RELATED MYOPATHY:
CLINICAL AND ULTRASTRUCTURAL INSIGHTS

Diego Lopercolo

19.30 - 19.45 IMPROVING MOLECULAR RESOLUTION IN NEUROMUSCULAR DISORDERS
WITH LONG-READ SEQUENCING

Pasquale Di Letto

19.45 - 20.00 TARGETED NGS NEWBORN SCREENING IN EUROPE:
FIRST RESULTS FROM THE SCREEN4CARE TREAT PANEL

Rita Selvatici

20.00 - 20.15 SYNTHETIC DATA FOR RESEARCH IN CIDP: VALIDATION AGAINST
REAL-WORLD DATA FROM THE ITALIAN CIDP REGISTRY

Pietro Emiliano Doneddu

20.15 - 21.45 **Welcome Cocktail**

Thursday, May 14th, 2026

*** PLENARY ROOM EUROPA

08.00 - 09.15 **Plenary Session**

Chairs: *Corrado Angelini, Stefania Corti*

Regeneration in neuromuscular disorders: from the pathogenic mechanism to new therapeutic approaches

Regeneration in neuromuscular disorders: the case of LGMDs

Giovanna Cenacchi

Pathophysiology of muscle regeneration and the satellite cell-opathies

Edoardo Malfatti

Stem cell-derived models and gene therapy approaches for neuromuscular regeneration

Stefania Corti

09.15 - 10.30 **Parallel Workshop 3 // #**

Chairs: *Fiore Manganelli, Elena Pegoraro*

Inherited neuromuscular diseases mimicking immune disorders

Hereditary neuropathies presenting with CIDP-like features

Marco Luigetti

Hereditary myopathies misdiagnosed as inflammatory myopathies

Carmelo Rodolico

Neuromuscular junction disorders: mistaking genetic for acquired

Raffaele Iorio

*** PARALELL ROOM ITALIA

09.15 - 10.30 **Parallel Workshop 4**

Chairs: *Alessandra Ariatti, Luca Bello*

AI in neurophysiology and imaging: automated signal analysis, MRI Radiomics, COMPASS project

Voice and AI in neuromuscular diseases

Raffaele Dubbioso

AI-Driven Patient Stratification in Undiagnosed Hereditary Neuromuscular Disorders: the CoMPaSS-NMD Experience

Rossella Ginevra Tupler

MRI in Muscle disorders

Giorgio Tasca

10.30 - 11.00 **Coffee Break**

••• PLENARY ROOM EUROPA

11.00 - 12.30 **ORAL COMMUNICATIONS**

Chairs: *Angelo Antonini, Renato Mantegazza, Rita Rinaldi*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

11.00 - 11.15 CLINICAL RESPONSE HETEROGENEITY TO FIRST-LINE BIOLOGIC THERAPIES IN ACHR-POSITIVE MYASTHENIA GRAVIS

Fiammetta Vanoli

11.15 - 11.30 IMPACT OF TARGETED THERAPIES ON THE DISEASE COURSE OF GENERALIZED MYASTHENIA GRAVIS

Rita Frangiamore

11.30 - 11.45 FUNCTIONAL CHARACTERIZATION OF ANTIBODIES DIRECTED AGAINST CLUSTERED ACETYLCHOLINE RECEPTOR

Gregorio Spagni

11.45 - 12.00 RITUXIMAB IN ACHR AND MUSK MYASTHENIA GRAVIS: LONG-TERM FOLLOW-UP WITH DIFFERENT THERAPEUTIC PROTOCOLS

Francesco Tuccillo

12.00 - 12.15 LATE-ONSET MYASTHENIA GRAVIS: CLINICAL PHENOTYPE AND LONGITUDINAL THERAPEUTIC MANAGEMENT IN A RETROSPECTIVE STUDY

Luca Angelini

12.15 - 12.30 COMPARATIVE EFFICACY OF ANTI-C5 VS. ANTI-FCRN THERAPY IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: A MULTICENTRE RETROSPECTIVE STUDY

Alba Cepele

••• MODULAR PARALLEL ROOM 1-2

11.00 - 12.30 **ORAL COMMUNICATIONS**

Chairs: *Dario Cocito, Matteo Garibaldi*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

11.00 - 11.15 LIMITATIONS OF STANDARD OF CARE THERAPY IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Claudia Lozi

11.15 - 11.30 ANTIBODIES AGAINST PROTEOLIPID PROTEIN-1 ARE IDENTIFIED IN PATIENTS WITH INFLAMMATORY NEUROPATHIES

Alberto De Lorenzo

Thursday, May 14th, 2026

- 11.30 - 11.45 WHEN DEMYELINATION IS NOT DEMYELINATION: RETHINKING NERVE CONDUCTION FINDINGS IN AUTOIMMUNE NODO/PARANODOPATHIES
Emanuele Cassano
- 11.45 - 12.00 LONG-TERM OUTCOME IN REFRACTORY ANTI-MAG ANTIBODY NEUROPATHY PATIENTS TREATED WITH BTK INHIBITORS
Benedetta Tierro
- 12.00 - 12.15 EVOLVING ELECTROPHYSIOLOGICAL PATTERNS IN CIDP: HOW ELECTROPHYSIOLOGICAL PATTERNS CAN INFORM TREATMENT RESPONSE AND RECOVERY
Rita Fiumarella
- 12.15 - 12.30 NEURALGIC AMYOTROPHY ULTRASOUND CHARACTERISTICS: A SINGLE CENTER STUDY
Sara Carta

... MODULAR PARALLEL ROOM 3

11.00 - 12.30 ORAL COMMUNICATIONS

Chairs: *Roberto Massa, Elena Saccani*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

- 11.00 - 11.15 OCULOPHARYNGEAL MUSCULAR DYSTROPHY: A MULTICENTER RETROSPECTIVE COHORT ANALYSIS FROM THE ITALIAN NETWORK
Claudia Alberti
- 11.15 - 11.30 THE NOVEL (TCTG)N MOTIF IN CNBP EXPANDED ALLELES: COMPOSITION, DYNAMICS AND GENOTYPE-PHENOTYPE CORRELATION IN DM2
Federica Centofanti
- 11.30 - 11.45 PLASMA PTAU-181 AS A PROGNOSTIC BIOMARKER OF MOTOR DECLINE IN MYOTONIC DYSTROPHY TYPE 1
Erica Frezza
- 11.45 - 12.00 CIRCULATING MUSCLE-SPECIFIC MIRNAS UNCOVER DIFFERENTIAL MOLECULAR SIGNATURES IN MYOTONIC DYSTROPHY TYPE 1 AND 2 PATIENTS
Dario Ciabini
- 12.00 - 12.15 INTEGRATED ORTHOPEDIC AND NEUROLOGICAL 14-YEAR EXPERIENCE IN THE DIAGNOSTIC APPROACH TO THE 'TOE WALKER' SPECTRUM IN A PEDIATRIC POPULATION
Federica Trentin

12.15 - 12.30 CLINICAL SPECTRUM OF MYOTONIC DYSTROPHY TYPE 2: RESULTS FROM A CROSS-SECTIONAL MONOCENTRIC STUDY

Elena Faedo

... PARALELL ROOM ITALIA

11.00 - 11.30 **Lecture sponsored by UCB Pharma | NO CME**

Chair: *Caterina Garone*

When to Suspect Thymidine Kinase 2 Deficiency (TK2d): Red Flags and Differential Diagnosis

Michelangelo Mancuso

11.30 - 12.00 **Lecture sponsored by Johnson&Johnson | NO CME**

Chair: *Rocco Liguori*

The evolving landscape of Myasthenia Gravis treatment: focus on nipocalimab

Carlo Antozzi

12.00 - 12.30 **Lecture sponsored by Argenx | NO CME**

Chair: *Rocco Liguori*

Rethinking When: Redefining Treatment Timing in Myasthenia Gravis

Yuri Matteo Falzone

12.30 - 13.30 **Lunch Buffet**

... MODULAR PARALLEL ROOM 1

12.45 - 13.30 ***Female carriers of muscular dystrophies**

... MODULAR PARALLEL ROOM 2

12.45 - 13.30 ***Myofibrillar and Distal Myopathies e Network distali**

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Thursday, May 14th, 2026

13.30 - 14.15 Symposium sponsored by Alexion | NO CME

Chairs: *Francesco Habetswallner, Rocco Liguori*

Clinical refractions in gMG: expanding ravulizumab and eculizumab evidence across all age groups

13.30 - 13.45 A Prism of Evidence for gMG: Integrating C5-inhibition treatment data from clinical trials in adult and pediatric patients
Paolo Emilio Alboini

13.45 - 14.00 Ravulizumab in late onset gMG: illuminating Real World outcomes
Laura Fionda

14.00 - 14.15 Through the Case Lens: Practical Management of gMG and Comorbidities
Daniele Velardo

14.15 - 15.00 Symposium sponsored by Roche | NO CME

Chair: *Marika Pane*

Spinal Muscular Atrophy lifespan: from newborn screening to adulthood

14.15 - 14.20 Introduction
Marika Pane

14.20 - 14.30 Born with SMA: early diagnosis and timely intervention
Marika Pane

14.30 - 14.40 Growing up with SMA: clinical transitions and phenotypic variability
Federica Ricci

14.40 - 14.50 Ageing with SMA: needs and clinical approaches of a chronic disease
Giulio Gadaleta

14.50 - 15.00 Discussion & Q&A
All Faculty

15.00 - 16.30 Poster Session | NO CME

16.30 - 17.00 Coffee Break

••• PLENARY ROOM EUROPA

17.00 - 18.30 **Parallel Workshop 5 // #**

Chairs: *Luca Padua, Giampietro Zanette*

Neuromuscular imaging in the diagnosis of inflammatory peripheral nerve and muscle disorders

Principles of neuromuscular ultrasound and clinical applications
Stefano Tamburin

Nerve Ultrasound in inflammatory neuropathies
Sara Carta

Muscle MRI in inflammatory myopathies
Silvia Nicolosi

••• PARALELL ROOM ITALIA

17.00 - 18.30 **Parallel Workshop 6**

Chairs: *Guido Angelo Cavaletti, Paola Mandich*

Schwann cell from normal to pathological conditions

Schwann Cells in the Development of the Peripheral Nervous System
Lucilla Nobbio

The Role of Beclin 1 and Autophagy/Endosome Trafficking in Myelination
Matilde Cescon

Neurovascular Interactions in Peripheral Nerve Regeneration and Degeneration
Dario Bonanomi

Therapeutic perspectives for Hereditary Neuropathies
Alessandra Bolino

••• MODULAR PARALLEL ROOM 1-2

17.00 - 18.00 ***Inflammatory Myopathies**

••• MODULAR PARALLEL ROOM 3

17.00 - 18.00 ***LGMD**

••• MODULAR PARALLEL ROOM 1-2

18.00 - 19.00 ***FSHD**

••• MODULAR PARALLEL ROOM 3

18.00 - 19.00 ***Myotonic Dystrophies**

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Thursday, May 14th, 2026

••• PLENARY ROOM EUROPA

18.30 - 20.00 **Parallel Workshop 7 // #**

Chairs: *Massimiliano Mirabella, Eduardo Nobile-Orazio*

Neuromuscular complications of oncologic immunotherapies

Introduction

Lucia Festino

Myopathies

Massimiliano Mirabella

Neuropathies

Paola Alberti

Myasthenia Gravis

Maria Pia Giannoccaro

••• PARALELL ROOM ITALIA

18.30 - 19.30 ***AIM Giovani**

••• MODULAR PARALLEL ROOM 1

19.00 - 20.00 ***AIG**

••• MODULAR PARALLEL ROOM 2

19.00 - 20.00 ***Mitochondrial Disorders**

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Friday, May 15th, 2026

••• PLENARY ROOM EUROPA

08.00 - 09.15 **Plenary Session**

Chairs: *Giacomo Pietro Comi, Antonella Pini*

Lessons from SMA treatments

Focus on novel approaches in SMA treatment

Eugenio Maria Mercuri

New evidence from transitional age and adulthood

Sonia Messina

From Genetic Diagnosis to Early-Treated SMA

Eduardo Fidel Tizzano Ferrari

09.15 - 10.30 **Parallel Workshop 8 // #**

Chairs: *Giovanni Meola, Davide Pareyson*

Repeats expansion

Myotonic Dystrophy type

Darren G. Monckton

Oculopharyngeal muscular dystrophy, RFC1-CANVAS

Andrea Cortese

Kennedy's disease

Maria Pennuto

••• PARALELL ROOM ITALIA

09.15 - 10.30 **Parallel Workshop 9**

Chairs: *Enrico Silvio Bertini, Lucia Ruggiero*

**Multisystem involvement in neuromuscular diseases
(myotonic dystrophy, Pompe disease, amyloidosis, mitochondrial diseases):
management for improved QoL**

Myotonic Dystrophies: new therapeutic approaches outcomes and clinical relevance

Valeria Sansone

ATTRv Polyneuropathy: management for improved QoL

Angelo Schenone

Management and Therapeutic options of patients with multisystem Pompe disease

Antonio Toscano

Friday, May 15th, 2026

10.30 - 11.00 **Coffee Break**

... PLENARY ROOM EUROPA

11.00 - 12.30 **ORAL COMMUNICATIONS**

Chairs: *Emily Bellone, Marco Savarese*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

11.00 - 11.15 A UNIVERSAL DONOR CELL FOR THE NEXT GENERATION CELL AND EX VIVO GENE THERAPIES

Giulio Cossu

11.15 - 11.30 PATIENT-DERIVED SPINAL CORD ORGANOID REVEAL CRITICAL TREATMENT WINDOWS IN SMA

Stefania Corti

11.30 - 11.45 MORPHOLOGICAL AND MOLECULAR ALTERATIONS IN THE SOMATOSENSORY CORTEX VASCULATURE OF RATS WITH PACLITAXEL-INDUCED PAINFUL PERIPHERAL NEUROPATHY

Valentina Alda Carozzi

11.45 - 12.00 ROLE OF UNCONVENTIONAL MYOSIN1B IN PERIPHERAL NERVOUS SYSTEM

Giovanna Capodivento

12.00 - 12.15 NEW INSIGHTS INTO THE MOLECULAR ROLE OF TNPO3 IN A ZEBRAFISH MODEL OF LGMDD2

Maria Teresa Rodia

12.15 - 12.30 THE MYOSTATIN-SMAD3 PATHWAY AS BIOMARKER FOR MONITORING DISEASE COURSE UNDER DISEASE-MODIFYING THERAPIES IN SPINAL MUSCULAR ATROPHY

Giorgia Riolo

... MODULAR PARALLEL ROOM 1-2

11.00 - 12.30 **ORAL COMMUNICATIONS**

Chairs: *Melania Giannotta, Marika Pane*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

11.00 - 11.15 MULTI-OMIC BIOMARKERS ENABLE PERSONALIZED SMA MANAGEMENT IN A MULTICENTER ITALIAN STUDY

Chiara Panicucci

- 11.15 - 11.30 SUSTAINED MOTOR FUNCTION STABILIZATION IN TREATED ADULT SPINAL MUSCULAR ATROPHY: REAL-WORLD EVIDENCE FROM PADOVA
Elena Sogus
- 11.30 - 11.45 DNA METHYLATION IN PERIPHERAL BLOOD AS A NEW POTENTIAL BIOMARKERS SMA
M'hammed Aguenouz
- 11.45 - 12.00 RESPIRATORY FUNCTION IN ADULT SMA PATIENTS AFTER LONG-TERM RISDIPLAM TREATMENT: THE EXPERIENCE OF ITALIAN CENTERS
Maria Sframeli
- 12.00 - 12.15 SMACK! PROJECT: IMPACT OF THE PARENT-CHILD INTERACTION IN THE EARLY NEURODEVELOPMENTAL STAGES OF A COHORT OF CHILDREN WITH SMA DIAGNOSED BY NEONATAL SCREENING - A PILOT STUDY
Stefano Parravicini
- 12.15 - 12.30 POLYGRAPHIC ASSESSMENT OF ADULT PATIENTS WITH SPINAL MUSCULAR ATROPHY FOLLOWING 12 MONTHS OF RISDIPLAM
Nicasio Rini

*** MODULAR PARALLEL ROOM 3

11.00 - 12.30 **ORAL COMMUNICATIONS**

Chairs: *Marcello Romano, Veria Vacchiano*

Each Presenting Authors will be given 13 minutes for presentation and 2 minutes for discussion

- 11.00 - 11.15 REFINING ELECTROPHYSIOLOGICAL CRITERIA IN CIDP AND MMN: TOWARD A UNIFIED DEFINITION OF MOTOR CONDUCTION BLOCK AND PROXIMAL TEMPORAL DISPERSION
Chiara Gallo
- 11.15 - 11.30 SMALL FIBER DYSFUNCTION IN FIBROMYALGIA: A MULTIMODAL STUDY
Domenico Dell'Aversana
- 11.30 - 11.45 NEUROPHYSIOLOGICAL ASSESSMENT IN PATIENTS WITH SPINAL MUSCULAR ATROPHY IDENTIFIED BY NEWBORN SCREENING
Riccardo Masson
- 11.45 - 12.00 LONG-TERM OUTCOMES AND NATURAL HISTORY OF SMALL FIBER NEUROPATHY
Grazia Devigili
- 12.00 - 12.15 DISEASE MODELLING IN DUCHENNE MUSCULAR DYSTROPHY - SINGLE-CENTRE PILOT STUDY USING A MACHINE LEARNING APPROACH
Federica Trucco
- 12.15 - 12.30 ELECTROPHYSIOLOGICAL EVIDENCE OF PRECLINICAL NON-LENGTH DEPENDENT SENSORY INVOLVEMENT IN TTR AMYLOIDOSIS
Mariagiovanna Castiglia

Friday, May 15th, 2026

... PARALELL ROOM ITALIA

11.00 - 11.30 **Lecture sponsored by Alfasigma | NO CME**

Chair: *Rocco Liguori*

Management of Pain and Motor Recovery in Peripheral Neuropathies
Stefano Tamburin

11.30 - 12.00 **Lecture sponsored by Argenx | NO CME**

Chair: *Vincenzo Donadio*

When Innovation converges: neuroimmunology at the intersection
Dario Ricciardi

12.00 - 12.45 **Symposium sponsored by Italfarmaco | NO CME**

Chairs: *Eugenio Maria Mercuri, Valeria Sansone*

**Givinostat: Advancing the Treatment Landscape
in Duchenne Muscular Dystrophy**

12.00 - 12.05 Introduction
Eugenio Maria Mercuri, Valeria Sansone

12.02 - 10.25 Givinostat: clinical evidence and long-term data
Luca Bello

12.25 - 12.45 Givinostat: translating evidence into clinical practice and patient management
Marika Pane

12.45 - 13.30 **Symposium sponsored by Avidity | NO CME**

Chair: *Valeria Sansone*

**Muscle Health: a holistic approach to Prepare for Tomorrow's
Therapeutic Innovations**

12.45 - 12.50 Introduction
Valeria Sansone

12.50 - 13.05 The importance of muscle health for long-term clinical outcomes
Valeria Sansone

13.05 - 13.12 Muscle as an endocrine system: multisystemic complexity
Sabrina Corbetta

13.12 - 13.22 A multidisciplinary focus on muscle health: MDT best-practice cases and chair-led discussion

Valeria Sansone, Sabrina Corbetta

13.22 - 13.30 Q&A

Valeria Sansone, Sabrina Corbetta

12.30 - 13.30 **Lunch Buffet**

... PARALLEL ROOM ITALIA

13.30 - 14.15 **Symposium sponsored by Biogen | NO CME**

Chair: *Giacomo Pietro Comi*

Towards a New Era: Emerging Perspectives in SMA Landscape

13.30 - 13.40 Welcome and Introduction

Giacomo Pietro Comi

13.40 - 13.55 Bridging Biology and the Clinic: Neuroprotection into Practice

Marika Pane

13.55 - 14.10 SMA Over Time: Clinical Insights from Long-Term Data and Emerging Biomarkers

Giulia Ricci

14.10 - 14.15 Q&A

All Faculty

14.15 - 15.00 **Symposium sponsored by UCB Pharma | NO CME**

Chair: *Lorenzo Maggi*

Generalized Myasthenia Gravis: from Complexity to Choice

14.15 - 14.20 Integrating patient expectations into the clinical decision-making framework for gMG management

Lorenzo Maggi

14.20 - 14.35 The patient who lives a different day every day: when sustained disease management becomes essential

Paolo Emilio Alboini

14.35 - 14.50 The patient seeking to regain voice and breath: when management is shaped by the waves of the disease

Raffaele Iorio

14.50 - 15.00 Interactive Discussion

All Faculty

Friday, May 15th, 2026

15.00 - 16.30 **Poster Session | NO CME**

16.30 - 17.00 **Coffee Break**

... PLENARY ROOM EUROPA

17.00 - 18.30 **Round Table Meeting** with Patient's Associations | NO CME**

*Chairs: Paola Mandich, Fiore Manganelli, Vincenzo Nigro,
Luisa Politano, Cristina Sancricca, Antonio Trabacca*

*** It is a roundtable discussion, providing an opportunity for AIM to present its various projects and updates to patients and patient associations, while also addressing any questions they may have.*

... PARALLEL ROOM ITALIA

17.00 - 18.30 **TRIVIAIM-ASNP Qualification Round | NO CME**

*Chairs: Luana Benedetti, Claudio Bruno,
Massimiliano Filosto, Serenella Serveidei*



... PLENARY ROOM EUROPA

18.30 - 19.30 **AIM General Assembly*** | NO CME**

... PARALLEL ROOM ITALIA

18.30 - 19.30 **ASNP General Assembly*** | NO CME**

20.30 - 24.00 **Social Dinner**

****AIM Members Assembly (Italian Association of Myology) and ASNP Members Assembly (Italian Association of Peripheral Nervous System), during which a report on the activities carried out by the Scientific Society throughout the year will be presented, along with the financial statement and plans for the upcoming year.*

Saturday, May 16th, 2026

... MODULAR PARALLEL ROOM 1

07.45 - 08.30 *Bone Health

... MODULAR PARALLEL ROOM 2

07.45 - 08.30 *Laminopathies Group

... MODULAR PARALLEL ROOM 3

07.45 - 08.30 *Rehabilitation and Long-Term Care

... PLENARY ROOM EUROPA

08.30 - 09.00 **Plenary Session // #**

Chair: *Tiziana Enrica Mongini*

LAMA2-related disease: when a gene hits muscle and nerve

S. Previtali

09.00 - 09.30 **Plenary Session // #**

Chair: *Vincenzo Nigro*

Lessons from Newborn Screening in SMA

Laurent Servais

09.30 - 10.45 **Parallel Workshop 10**

Chairs: *Francesco Habetswallner, Anna Mazzeo*

Neuropathy and autoimmune myasthenia

Introduction: autoimmune neuropathies

Chiara Briani

What therapy for what patient? Personalizing treatment choices
in myasthenia gravis

Lorenzo Maggi

Novel and emerging treatment in autoimmune neuropathies

Pietro Emiliano Doneddu

Italian Recommendations for the Diagnosis and Treatment of Myasthenia
Gravis - 2025 Update

Laura Fionda

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Saturday, May 16th, 2026

... PARALELL ROOM ITALIA

09.30 - 10.45 **Parallel Workshop 11 // #**

Chairs: *Gian Maria Fabrizi, Serenella Servidei*

Nerve and muscle involvement in complex genetic diseases

Peripheral neuropathy in complex inherited disorders
Massimiliano Filosto

Beyond muscle weakness in muscle disorders
Giovanna Lattanzi

Nerve and muscle involvement in mitochondrial disorders
Olimpia Musumeci

10.45 - 11.15 **Coffee Break**

... PLENARY ROOM EUROPA

11.15 - 12.15 **TRIVIAIM-ASNP Contest Final | NO CME**

Chairs: *Luana Benedetti, Claudio Bruno,*
Massimiliano Filosto, Serenella Servidei



12.15 - 13.45 **Closing Ceremony & Awards**

WEDNESDAY, MAY 13TH, 2026**16:30-18:00****ORAL COMMUNICATIONS SESSION N.1****Plenary Room Europa****Chairs: Alessandra Ferlini, Federica Ricci****MUSCULAR DYSTROPHIES****Abstract Cod. 143424****NONSENSE VARIANTS IN BECKER MUSCULAR DYSTROPHY: CLINICAL COURSE AND DISEASE SEVERITY**

Gorgoglione D.^{*1}, Sabbatini D.¹, Riguzzi P.¹, Capece G.¹, Petrosino A.¹, Vianello S.¹, Panicucci C.², Latinakis G.², Morando S.², Traverso M.⁴, Gadaleta G.³, D'Alessandro R.⁵, Urbano G.³, Cavallina I.⁵, Rolle E.³, Ricci F.⁵, Pane M.⁶, Palermo C.⁶, Stanca G.⁶, Ruggiero L.⁷, Zoppi D.⁷, Russo A.⁷, De Maria M.⁷, D'Angelo M.G.⁸, Diella E.⁸, Servidei S.⁹, Briganti M.¹⁰, Sancricca C.¹⁰, D'Amico A.¹¹, Catteruccia M.¹¹, Penzo M.¹², Bruschi F.¹², Ardisson A.¹², Parravicini S.¹², Masson R.¹², Gallone A.¹³, Maggi L.¹³, Giannotta M.¹⁴, Briganti E.¹⁴, Valentino M.L.¹⁴, Marinella G.¹⁵, Gardani A.¹⁶, Pratile D.C.¹⁷, Iosca A.¹⁶, Dainesi M.L.¹⁶, Zambon A.A.¹⁸, Torri F.¹⁹, Ricci G.¹⁹, Sframeli M.²⁰, Allegra C.²⁰, Albamonte E.²¹, Maroni S.²¹, Maiorano S.²¹, Magri F.²², Velardo D.²², Lerario A.²², Picillo E.²³, Politano L.²⁴, Passamano L.²⁴, Scutifero M.²⁴, Nigro V.²³, Comi G.²⁵, Sansone V.A.²¹, Messina S.²⁰, Siciliano G.¹⁹, Previtali S.¹⁸, Berardinelli A.¹⁶, Battini R.¹⁵, Pini A.¹⁴, Moroni I.¹², Mercuri E.⁶, Mongini T.E.³, Bruno C.², Bello L.¹, Pegoraro E.¹

¹ Department of Neurosciences, Neuromuscular Center, University of Padova, Padova, Italy, ² Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, Italy, ³ Neuromuscular Unit, Department of Neurosciences RLM, University of Torino, Torino, Italy, ⁴ Medical Genetics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy, ⁵ Child Neuropsychiatry Unit, Department of Public Health and Pediatric Sciences, Torino, Italy, ⁶ Centro Clinico Nemo Pediatrico, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy, ⁷ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Napoli, Italy, ⁸ Unit of Rare Diseases of the Central and Peripheral Nervous System, Scientific Institute IRCCS Eugenio Medea, Bosisio Parini, Italy, ⁹ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italy, ¹⁰ Neuro-rehabilitation center, Fondazione UILDM Lazio ETS, Roma, Italy, ¹¹ IRCCS, Unit of Muscular and Neurodegenerative disorders, Bambino Gesù Children's Hospital, Roma, Italy, ¹² Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Milano, Italy, ¹³ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Milano, Italy, ¹⁴ IRCCS Istituto delle Scienze Neurologiche di Bologna, Neuromuscular Pediatric Unit, Bologna, Italy, ¹⁵ Department of Developmental Neuroscience, IRCCS Fondazione Stella Maris, Pisa, Italy, ¹⁶ IRCCS Mondino Foundation, Pavia, Italy, ¹⁷ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, ¹⁸ Neurology

Unit, IRCCS Ospedale San Raffaele, Milano, Italy, ¹⁹ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ²⁰ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ²¹ The NEMO Clinical Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Milano, Italy, ²² Neuromuscular and Rare Disease Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ²³ Medical Genetics and Cardiomyology, Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Napoli, Italy, ²⁴ Cardiomyology and Medical Genetics, University of Campania 'Luigi Vanvitelli', Napoli, Italy, ²⁵ Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Nonsense variants in Becker muscular dystrophy (BMD) are exceedingly rare but represent about 10-12% of small variants in Duchenne muscular dystrophy (DMD).

We present a large cohort of nonsense-BMD aimed to identify clinical severity and possibly dystrophin "rescue" mechanisms. Twenty-nine nonsense-BMD patients from a cohort of 458 BMD patients were evaluated using the North Star Ambulatory Assessment (NSAA), 6-minute walk test (6MWT), Medical Research Council (MRC) scale, Performance of Upper Limb (PUL) 2.0, and left ventricular ejection fraction (LVEF). Genetic data were collected, and in silico analyses were performed to investigate potential splicing effects.

The mean age at last assessment was 35.6±16.7 years, with a median [IQR] age at diagnosis of 11.9 [6.5-24] years. Nine patients (31%) lost ambulation, with an estimated median age of 52 years. Despite wide clinical variability, patients showed a median NSAA score (0-34) of 33 [28-34] and a mean 6MWT distance of 335.6m±267m with a significant annual decline of 0.38 points (SE 0.10; p < 0.001) and 6.7m/year (SE 2.4; p = 0.005), respectively. No significant differences in NSAA score or walking distance were observed between ambulant patients with nonsense variants and the overall BMD cohort. A 59% of patients showed LVEF% < 55%. Finally, in silico analyses suggested in a subset of variants creation of splicing silencer motifs and activation of a novel donor splice site. This study highlights the clinical heterogeneity of BMD associated with nonsense variants, providing new insights into this extremely rare population. Improved knowledge of dystrophin "rescue" mechanisms may inform prognostic assessment and therapeutic strategies.

DUCHENNE MUSCULAR DYSTROPHY (DMD)**Abstract Cod. 143085****DUCHENNE MUSCULAR DYSTROPHY DRIVES**

T CELL REMODELING

Villa C.^{*1}, Farini A.², Torrente Y.²

¹ Stem Cell Laboratory, Department of Pathophysiology and Transplantation, Dino Ferrari Centre, Università degli Studi di Milano, Milan, Italy, Milano, Italy, ² Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, Milano, Italy

Duchenne muscular dystrophy (DMD) is characterized by progressive muscle degeneration, yet systemic immunological consequences remain poorly understood. Recent fatalities following AAV-mediated gene therapy highlight critical gaps in baseline immune dysfunction knowledge. This study aimed to comprehensively characterize systemic immune profiles in glucocorticoid-free DMD patients using multi-omic approaches.

We performed single-cell transcriptomic and epigenomic profiling coupled with systemic cytokine analysis in glucocorticoid-free DMD patients. Immune cell populations were characterized across bone marrow, dystrophic muscle, and peripheral blood compartments. Cell-cell communication networks were analyzed, and findings were validated through meta-analysis across independent cohorts.

DMD exhibited distinct immune microenvironments: bone marrow harbored transcriptionally primed yet phenotypically naïve lymphocytes with stress-responsive signatures (ATF3, FOSB) and metabolic reprogramming. Dystrophic muscle showed chronic T cell exhaustion with epigenetic imprinting. Paradoxically, circulating CD8⁺ memory T cells maintained TCF1+TIGIT[−] stem-like features despite tissue exhaustion. Systemic profiling revealed elevated pro-inflammatory mediators (IL-6, TNF receptors, interferons) with impaired chemokine networks. Bone marrow networks centered on monocyte-mediated T cell priming, while muscle networks involved FAP-myofiber-macrophage triads driving remodeling.

Pre-existing immune priming in DMD—characterized by stress-responsive transcription, enhanced OXPHOS metabolism, and preserved T cell stemness—may predispose patients to exaggerated therapeutic responses, providing essential groundwork for predicting complications and designing immunomodulatory strategies.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract Cod. 143363

CHARACTERIZING INITIAL SYMPTOMS AND FUNCTIONAL EVOLUTION IN BECKER MUSCULAR DYSTROPHY

Petrosino A.^{*1}, Gorgoglione D.¹, Sabbatini D.¹, Riguzzi P.¹, Capece G.¹, Sogus E.¹, Fornasier T.¹, Vianello S.¹, Panicucci C.², Latinakis G.², Morando S.², Traverso M.³, Gadaleta G.⁴, D'Alessandro R.⁴, Urbano G.⁴, Cavallina I.⁴, Rolle E.⁴, Ricci F.⁴, Pane M.⁵, Palermo C.⁵, Stanca G.⁵, Ruggiero L.⁶, Zoppi D.⁶, Russo A.⁶, De Maria M.⁶, D'Angelo M.G.⁷, Diella E.⁷, Servidei S.⁸, Briganti M.⁹, Sancricca C.⁹, D'Amico A.¹⁰, Catteruccia M.¹⁰, Penzo M.¹¹, Bruschi F.¹¹, Ardisson A.¹¹, Parravicini S.¹¹, Masson R.¹¹, Gallone A.¹², Maggi L.¹², Giannotta M.¹³, Briganti E.¹³, Valentino M.L.¹³, Marinella G.¹⁴, Gardani A.¹⁵, Iosca A.¹⁵, Pratile D.C.¹⁵, Dainesi M.I.¹⁵, Zambon A.¹⁶, Torri F.¹⁷, Ricci G.¹⁷, Sframeli M.¹⁸, Allegra C.¹⁸, Albamonte E.¹⁹, Maroni S.¹⁹, Maiorano S.¹⁹, Magri F.²⁰, Velardo D.²⁰, Lerario A.²⁰,

Picillo E.²¹, Politano L.²², Passamano L.²², Scutifero M.²², Nigro V.²¹, Comi G.²⁰, Sansone V.¹⁹, Messina S.¹⁸, Siciliano G.¹⁷, Previtali S.¹⁶, Berardinelli A.¹⁵, Battini R.¹⁴, Pini A.¹³, Moroni I.¹¹, Mercuri E.⁵, Mongini T.E.⁴, Bruno C.², Bello L.¹, Pegoraro E.¹

¹ Department of Neurosciences, Neuromuscular Center, University of Padova, Padova, Italy, ² Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, Italy, ³ Pediatric Neurology and Muscle Disease Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy, ⁴ Neuromuscular Unit, Department of Neurosciences RLM, University of Torino, Turin, Italy, ⁵ Centro Clinico Nemo Pediatrico, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy, ⁶ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Naples, Italy, ⁷ Unit of Rare Diseases of the Central and Peripheral Nervous System, Scientific Institute IRCCS Eugenio Medea, Bosisio Parini, Italy, ⁸ Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ⁹ Neuro-rehabilitation center, Fondazione UILDM Lazio ETS, Rome, Italy, ¹⁰ IRCCS, Unit of Muscular and Neurodegenerative disorders, Bambino Gesù Children's Hospital, Rome, Italy, ¹¹ Department of Pediatric Neuroscience, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Milan, Italy, ¹² Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico 'Carlo Besta', Milan, Italy, ¹³ IRCCS Istituto delle Scienze Neurologiche di Bologna, Neuromuscular Pediatric Unit, Bologna, Italy, ¹⁴ Department of Developmental Neuroscience, IRCCS Fondazione Stella Maris, Pisa, Italy, ¹⁵ Child and Adolescence Neuromuscular Disorders Research Section, IRCCS Mondino Foundation, Pavia, Italy, ¹⁶ Neuromuscular Repair Unit, Division of Neuroscience, Institute of Experimental Neurology (InSpe), IRCCS Ospedale San Raffaele, Milan, Italy, ¹⁷ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ¹⁸ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ¹⁹ The NEMO Clinical Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Milan, Italy, ²⁰ Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, ²¹ Medical Genetics and Cardiomyology, Department of Precision Medicine, University of Campania 'Luigi Vanvitelli', Napoli, Italy, ²² Cardiomyology and Medical Genetics, University of Campania 'Luigi Vanvitelli', Napoli, Italy

Becker muscular dystrophy (BMD) is a rare progressive neuromuscular disorder caused by variants in the DMD gene, characterized by marked heterogeneity in age at onset and presenting symptoms. Longitudinal data were collected from 326 BMD patients followed by 16 Italian neuromuscular centres, including demographics, age at symptom onset and diagnosis. Diagnostic delay was evaluated according to presenting symptoms. Motor function was assessed using the North Star Ambulatory Assessment (NSAA) and the 6-minute walk test (6MWT) at 12, 24 and 36 months from baseline.

Mean age at baseline was 25.1±15.3 years, with mean age at onset of 7.5±7.7 years and mean age at diagnosis of 9.7±10.7 years, yielding a mean diagnostic delay of 2.1±6.8 years. Patients were categorized by first symptom: motor, incidental hyperCKemia (CK), pseudometabolic, cardiac and other. CK was the initial sign in 46% of patients (149). At baseline, patients presenting with motor symptoms had significantly lower NSAA scores than CK ($p = 7.6 \times 10^{-12}$), pseudometabolic ($p = 1.1 \times 10^{-7}$) and other ($p = 4.0 \times 10^{-3}$), with medians [IQR] of 20.5 [11–33], 34 [33–34], 34 [31–34] and 33.5 [28–34], respectively. These differences were confirmed after adjusting for age, which was negatively correlated with NSAA ($p < .0001$). Functional trajectories over 36 months showed no significant differences between groups. A similar pattern was observed for 6MWT performance.

A better understanding of early disease manifestations and their relationship with diagnostic delay and functional trajectories is essential to improve patient stratification and to inform the design of natural history studies and clinical trials.

Abstract Cod. 143020

EVOLUTION OF SWALLOWING DISTURBANCES IN DUCHENNE MUSCULAR DYSTROPHY (DMD)

Legnani C., Amorelli V., Brambilla D., Decio A., Lavatelli R., Marelli S., Cima R., Maiocchi V., Landoni V., D'Angelo M.G.*
Scientific Institute IRCCS E. Medea-Ass. La Nostra Famiglia, Bosisio Parini (Lecco), Italy

In DMD, dysphagia is a consequence of the impairment of oropharyngeal striated muscles function, leading a slower and effortful bolus transportation and of the tongue hypertrophy generating malocclusions and decreasing chewing efficiency.

We collected longitudinal data of a group of DMD patients, focusing our attention on the speech therapist evaluation of the meal and the MASA (Mann Assessment Swallowing Ability scale).

68 DMD subjects (16.88 +/- 7.16 years; 4 - 34) were included. According to MASA scores and clinical evaluation, no signs of chewing alterations were observed in 4 subjects at the age of 9.75 +/- 5.74 years; mild alterations were documented at the age of 12.10 +/- 5.57 yrs, when % FVC predicted was 71.87 +/- 24.74; while a mild dysphagia was observed at the age of 17.73 +/- 5.72 years, with % FVC 43.51 +/- 24.52 predicted.

A moderate dysphagia was present at 21.34 +/- 5.7 years, when % FVC was 31 +/- 28.29. A moderate-severe dysphagia with risk of aspiration was reported in patients aged 26 +/- 4.35, supported by NIV > 18 hours a day with FVC% predicted of 10 +/- 4.3. A severe dysphagia was recorded in NIV dependent subjects, aged 28 +/- 3.74 years. Nutritional status deteriorated over time, and most boys with moderate or severe dysphagia were underweight or malnourished while the frequency of respiratory infections increased.

Early signs of chewing and swallowing alterations with a linear decrease over time are observed, suggesting early evaluation and monitoring of the swallowing function.

Alteration in chewing and swallowing capability, nutritional status and chronic respiratory insufficiency are closely related.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract Cod. 143351

PROSPECTIVE EVALUATION OF SLEEP-DISORDERED BREATHING AND FUNCTIONAL ASSESSMENT IN DUCHENNE MUSCULAR DYSTROPHY: DYSTREST STUDY

Maccarrone A.¹, Chiarella L.², Brolatti N.³, Morando S.³, Gizzi G.⁴, Cordani R.², Iadarola A.⁵, Veneruso M.², Panicucci C.³, Minetti C.⁵, Ruggieri M.⁶, Bruno C.⁷, Striano P.⁸, Nobili L.², Pedemonte M.*4, Trucco F.⁸

¹ 1. Unit of Pediatric Clinic, Department of Clinical and Experimental Medicine, University of Catania, Catania, 95100, Italy 2. Pediatric

Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy, Catania, Italy, ² 3. Child Neuropsychiatry Unit, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy 4. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, 16147, Italy, Genova, Italy, ³ 5. Centre of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy, Genova, Italy, ⁴ 2. Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy, Genova, Italy, ⁵ 4. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, 16147, Italy, Genova, Italy, ⁶ 1. Unit of Pediatric Clinic, Department of Clinical and Experimental Medicine, University of Catania, Catania, 95100, Italy, Catania, Italy, ⁷ 4. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, 16147, Italy 5. Centre of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy, Ge, ⁸ 2. Pediatric Neurology and Muscular Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, 16147, Italy 4. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, Genova, 16147, Italy, Geno

Sleep-disordered breathing (SDB), including nocturnal hypoventilation (NH), is a recognized complication in Duchenne muscular dystrophy (DMD). Its association with motor and respiratory decline is poorly defined. This study aims to characterize sleep disorders in DMD and their potential as disease biomarker.

DystREST is an ongoing prospective, single-center observational study. Participants underwent pulmonary and motor assessments, overnight cardiorespiratory polygraphy (PG) with transcutaneous gas monitoring, sleep/circadian rhythm evaluation using questionnaires, actigraphy and salivary melatonin. Clinical variables including genotype, ambulatory status, age at loss of ambulation (LOA), and therapies were correlated to sleep measures.

Twenty patients were included, 13/20 non-ambulant, 7/20 on nocturnal ventilation. Median (IQR) age was 17.2 years (14.8-23.6). None of the patients had NH; SDB was detected in 3/20 patients, 2/3 being non-ambulant. Events were mainly obstructive in nature. In non-ventilated patients, those with SDB had lower average FVC% pred. compared to those without SDB. No significant association was found between SDB severity and motor or pulmonary function.

Subjective daytime sleepiness and chronotype analysis were overall within normal limits. However, 7/20 patients reported insufficient sleep quality, and actigraphy revealed an average daytime sleep duration exceeding one hour in three patients. Subjective daily sleepiness positively correlated with SDB severity ($p = 0.048$).

Our preliminary results contribute to sleep characterization in DMD. They suggest that standard criteria to quantify SDB may not reflect disease severity. Further ongoing analysis using diaphragm-specific PG metrics may improve phenotypic characterization and support sleep as a stage-specific biomarker in DMD.

EXPERIMENTAL THERAPIES

Abstract Cod. 143368

CELL-MEDIATED EXON SKIPPING INDUCES ROBUST DYSTROPHIN EXPRESSION AT A VERY LATE-STAGE OF DUCHENNE MUSCULAR

DYSTROPHY

Previtali S.C.^{*1}, Zambon A.², Tucci F.², Mierzejewski B.², Montini E.², Torrente Y.³, Aiuti A.¹, Cossu G.⁴

¹ Vita-Salute San Raffaele University, Milano, Italy, ² IRCCS Ospedale San Raffaele, Milano, Italy, ³ Centro Dino Ferrari, University of Milan, Milano, Italy, ⁴ Division of Cell Matrix Biology & Regenerative Medicine FBMH, University of Manchester., Manchester, United Kingdom

Duchenne muscular dystrophy (DMD) is a severe, progressive muscle disease for which effective therapies are still lacking. Gene therapy and exon-skipping approaches have not yet achieved curative efficacy, and previous cell-therapy attempts were limited by poor cell engraftment.

We report the safe transplantation of autologous myogenic cells obtained from a foot muscle of a non-ambulant DMD patient amenable to exon-51 skipping. Patient-derived mesoangioblasts were transduced with a lentiviral vector expressing a small nuclear RNA engineered to induce skipping of dystrophin exon 51. Twenty million cells, suspended in 2 mL of PBS, were injected into the extensor digitorum brevis muscle. Muscle tissue was analyzed three months after transplantation

Despite extensive fibrosis and fatty infiltration of the recipient muscle, transplanted cells generated new muscle fibers expressing dystrophin and α -sarcoglycan, accounting for 35% and 50%, respectively, of the remaining muscle fibers. Dystrophin protein was detectable in post-treatment samples but not in pre-treatment muscle.

These findings suggest that cell-mediated exon-skipping may be effective in pediatric DMD patients. Moreover, strategies aimed at reducing fibrosis may allow therapeutic intervention even in severely affected dystrophic muscles.

WEDNESDAY, MAY 13TH, 2026

16:30-18:00

ORAL COMMUNICATIONS SESSION N.2

Plenary Room Italia

Chairs: Mauro Monforte, Maria Lucia Valentino

MUSCULAR DYSTROPHIES

ABSTRACT COD. 142980

PROGRESSION DYNAMICS AND DISABILITY MILESTONES IN CHILDHOOD-ONSET FSHD

Ravera B.^{*1}, Di Marco C.¹, Barreto--Haagsma A.², Bortolani S.³, Torchia E.¹, Muni--Lofra R.², Diaz--Manera J.², Guglieri M.², Marini--Bettolo C.², Straub V.², Leone D.⁴, Pane M.⁴, Mercuri E.⁴, Ricci E.⁴, Monforte M.³, Tasca G.²

¹ Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy, Roma, Italy, ² John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle

Hospitals NHS Foundation Trusts, Newcastle Upon Tyne, UK, Newcastle Upon Tyne, United Kingdom, ³ Unità Operativa Complessa di Neurologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy, Roma, Italy, ⁴ Centro Clinico NeMO, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Rome, Italy, Roma, Italy

Childhood-onset FSHD1 shows marked clinical heterogeneity, and predictors of early functional decline remain incompletely defined. We aimed to identify baseline factors associated with major lower-limb disability milestones and with the speed of progression once lower-limb involvement occurred.

We analyzed longitudinal and cross-sectional data of patients with FSHD1 onset before age 18 from Policlinico Gemelli of Rome and the John Walton Muscular Dystrophy Research Centre in Newcastle upon Tyne. Two time-to-event outcomes were defined using the Clinical Severity Scale (CSS): lower-limb involvement (CSS ≥ 3) and loss of independent ambulation (LOIA; CSS ≥ 4.5). We assessed associations with baseline variables including sex, D4Z4 repeat length, age at onset, family history and symptom at onset. Progression speed was analyzed among patients with established lower-limb involvement to loss of independent ambulation.

The total cohort included 104 patients (mean follow-up 13 years). Short D4Z4 repeat length (1–3 vs 7–9) was the strongest independent risk factor for earlier LOIA (HR $\approx$ 5.6, $p = 0.009$) and lower-limb involvement (HR $\approx$ 2.5, $p = 0.012$). Negative family history independently increased LOIA risk (HR $\approx$ 2.3, $p = 0.034$). Faster progression was independently associated with de novo cases (HR 3.50, $p = 0.022$) and a facial onset pattern (vs scapular; HR 3.91, $p = 0.038$).

In this childhood-onset FSHD1 cohort, genetics influenced the risk of major disability milestones, while familial versus sporadic disease background and early phenotype shaped progression speed after lower-limb involvement. These findings highlight the complexity of childhood-onset FSHD1 progression and underscore the need for larger studies to develop prognostic markers.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract Cod. 143050

AN INTEGRATED LONG-READ SEQUENCING WORKFLOW FOR COMPREHENSIVE MOLECULAR CHARACTERIZATION OF FSHD PATIENTS

Strafella C.^{*1}, Megalizzi D.¹, Trastulli G.¹, Proietti Piorgo E.¹, Colantoni L.¹, Peconi C.¹, Ingrassi A.¹, Cascella R.¹, Sapia V.B.², Ebadi P.³, Gasparotto E.³, Favalli V.³, Giardina E.¹

¹ UOC Diagnostica di Laboratorio e Genomica Medica, Santa Lucia Foundation IRCCS, Rome, Italy, ² Arrow Diagnostics S.R.L., Genova, Italy, ³ 4bases S.R.L., Pavia, Italy

The molecular diagnosis of facioscapulohumeral muscular dystrophy (FSHD) is challenged by the intrinsic limitations of standard assays in fully characterizing the 4q35 locus. Advanced sequencing technologies now provide an opportunity to improve the molecular resolution of FSHD testing.

This study aimed to establish a long-read sequencing (LRS)-based

protocol coupled with a dedicated bioinformatic pipeline to simultaneously assess D4Z4 repeat size and methylation levels, 4q haplotype, and the presence of variants in FSHD2-associated genes.

High-molecular-weight DNA was extracted from peripheral blood using the Puregene Blood Kit (Qiagen). Libraries were prepared from 2.5 µg of DNA using the Ligation Sequencing Kit V14 (SQK-LSK114), and 600 ng of library was loaded onto a PromethION flow cell and sequenced for 72 hours on a PromethION platform (Oxford Nanopore Technologies).

The bioinformatic workflow (4eVAR) was developed using specific anchors and molecular markers (p13E-11, pLAM, PAS, and 4q/10q telomeric signatures) to selectively extract informative long reads, enabling identification of permissive 4qA alleles and accurate D4Z4 size estimation. The pipeline also enabled direct 5-methylcytosine detection and identification of FSHD2-related variants through long-read alignment, variant calling, and annotation. The protocol was evaluated in a pilot cohort of six patients with FSHD and compared with results obtained using standard methods. High concordance was observed across all parameters in all the tested samples.

Although validation in larger cohorts is required, these results indicate that an integrated LRS-based workflow may provide a feasible single-assay approach for comprehensive molecular characterization of both FSHD1 and FSHD2, potentially reducing turnaround times and diagnostic complexity.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract Cod. 143435

INNATE IMMUNE ACTIVATION ASSOCIATED WITH MUSCLE-SPECIFIC FRG1 OVEREXPRESSION

Fantini S.^{*1}, Bisceglia G.¹, Zyla J.², Moio N.¹, Termanini A.³, Nuredini A.¹, D'Antona G.⁴, Vattemi G.⁵, Malfatti E.⁶, Polanska J.², Tupler R.¹

¹ University of Modena and Reggio Emilia, Modena, Italy, ² Department of Data Science and Engineering, Silesian University of Technology, Gliwice, Poland, ³ Human Technopole, Milano, Italy, ⁴ CRIAMS-Sport Medicine Centre Voghera University of Pavia, Voghera, Italy, ⁵ Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, ⁶ Reference Center for Neuromuscular Disorders, APHP Henri Mondor University Hospital, Université Paris Est Créteil, INSERM, U955, IMRB, Créteil, France

The pathogenic mechanism(s) at the basis of facioscapulohumeral muscular dystrophy (FSHD) has been primarily associated with anomalous expression of the retrogene DUX4. However, this model displays several pitfalls including the recent discovery that primer sets widely employed for DUX4 detection amplify multiple loci beyond 4q/10q. This incomplete knowledge has prevented the development of effective disease-modifying therapies.

Consequently, robust preclinical models are needed to elucidate disease mechanisms and to evaluate novel therapeutic approaches.

We investigated the contribution of FSHD Region Gene 1 (FRG1), located at 4q35, to disease pathogenesis using a longitudinal multi-

omics approach to define molecular and cellular events driving muscle degeneration and to assess the therapeutic relevance of immune modulation.

Skeletal muscle overexpression of FRG1, encoding an RNA-binding protein, produced a progressive dystrophic phenotype resembling human FSHD, characterized by fiber size variability, necrosis, central nucleation, and connective tissue expansion. Integrated longitudinal analyses revealed progressive enrichment of innate immune pathways, particularly interferon and complement signaling, accompanied by macrophage infiltration and expansion of fibroadipogenic progenitors in severely affected muscle. By reducing the inflammatory response, we observe an amelioration of the FRG1-associated muscle phenotype, including a significant slowing of disease progression.

In conclusion, heterochronic induction of FRG1 is sufficient to drive a myopathic phenotype that can be treated. Collectively, these findings provide new insights into the molecular mechanisms underlying muscular dystrophies and point at immune modulation as a potential novel therapeutic strategy for FSHD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract Cod. 143036

RETHINKING GENOMICS OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN THE TELOMERE-TO-TELOMERE ERA: PITFALLS IN THE HIDDEN LANDSCAPE OF D4Z4 REPEATS

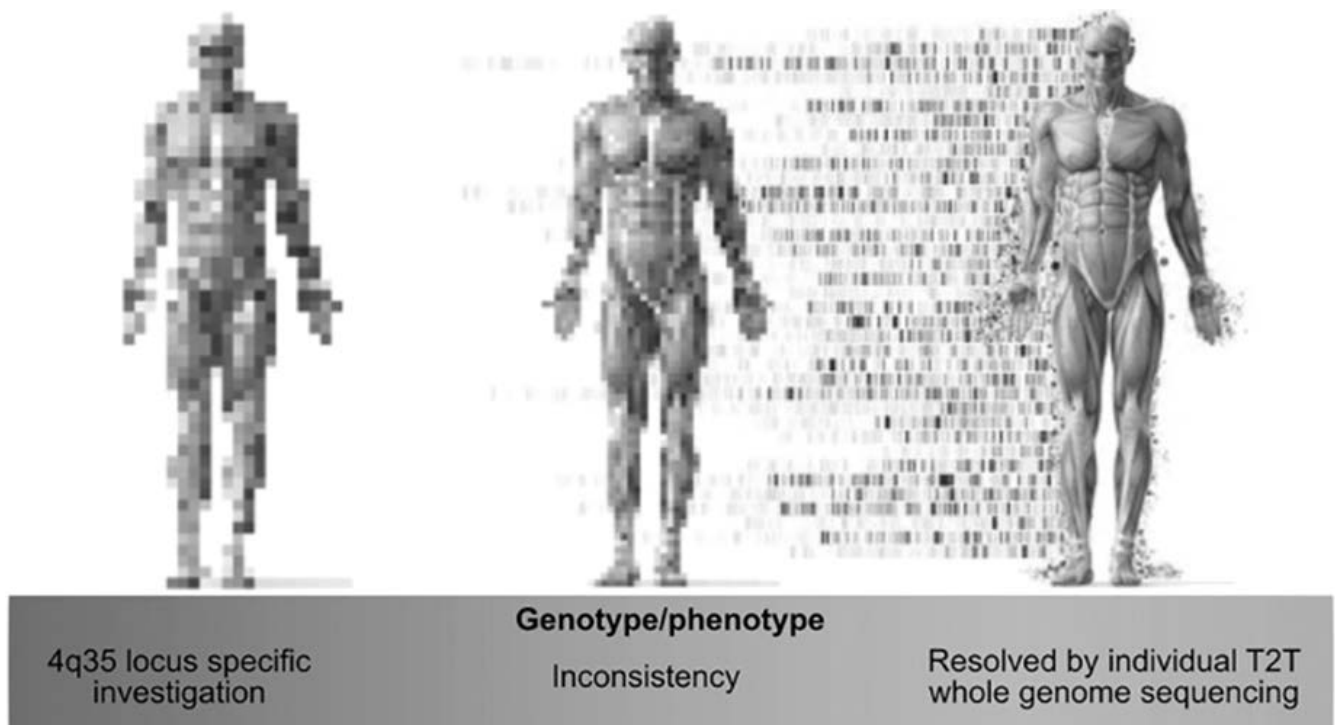
Salsi V.¹, Losi F.¹, Pini S.^{*1}, Horner D.², Chiara M.², Tupler R.¹

¹ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, ² Department of Biosciences, University of Milan, Milan, Italy

Facioscapulohumeral muscular dystrophy (FSHD) is genetically associated with reduction of the D4Z4 macrosatellite array at 4q35 on a permissive 4qA haplotype, a configuration that enables the stable expression of the DUX4 transcription factor. Current diagnostic and mechanistic models, however, rely heavily on the incomplete GRCh38/hg38 reference and assume that D4Z4 repeats are predominantly confined to 4q35 and 10q26 loci.

Here we present a systematic re-analysis of the configuration and evolution of D4Z4-like repeats based on the Telomere-to-Telomere human genome assembly (T2T-CHM13 v2.0/hs1), T2T assemblies from the Human Pangenome Reference Consortium and several monkeys and primates. We also provide complementary experimental validation: using the terminal 4q35 repeat as a query, we annotated the full repertoire of D4Z4-like loci across the genomes and characterized their structural completeness, flanking sequences, and coding potential.

This survey uncovered complete D4Z4 repeats as well as partial sequences organized as clusters or isolated monomers on at least ten additional chromosomes, several of which harbor intact DUX4 open reading frames or polyadenylation signals. Considering our findings, we also tested the specificity of several assays commonly used in FSHD research and diagnostics. Together, our data demonstrates that



many signals historically attributed to the pathogenic 4q locus may in fact arise from paralogous arrays.

Our study establishes the necessity of locus-resolved, repeat-aware approaches, combining long-read sequencing and methylation profiling, and isoform-resolved transcriptomics, for accurate diagnostics and to define the molecular basis of FSHD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract Cod. 143355

A TELOMERIC TRANSLOCATION CAUSING FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY IN A FAMILY WITH NORMAL D4Z4 SIZE

Quartesan I.^{*1}, Facchini S.¹, Lemmers R.J.², Efthymiou S.¹, Dominik N.¹, Van Der Vliet P.J.², Tasca G.³, Cortese A.¹, Van Der Maarel S.M.², Straub V.³, Bugiardini E.¹

¹ Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ² Department of Human Genetics, Leiden University Medical Center, Leiden, Netherlands, ³ John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom

Facioscapulohumeral muscular dystrophy (FSHD) results from aberrant DUX4 expression due to D4Z4 chromatin relaxation, caused by repeat contraction (FSHD1) or mutations in chromatin repressors like SMCHD1 (FSHD2). While standard testing confirms diagnosis in the vast majority cases, a small subset of patients with clinically FSHD remains unsolved, suggesting that pathogenic mechanisms not de-

tected by conventional diagnostics may exist, and require advanced technologies to be uncovered.

To identify the genetic cause in a familial case with highly suggestive FSHD features but negative extensive genetic workup.

Two affected siblings presented with asymmetric shoulder girdle and distal leg weakness, scapular winging, and variable facial involvement. Muscle MRI showed typical FSHD pattern. Southern blotting, methylation analysis, and WGS neuromuscular panels were negative for FSHD1, FSHD2, and other neuromuscular disorders. Optical genome mapping (OGM) in both affected and one unaffected sibling detected a 4q-7 translocation on the 4qA-17 allele, present only in affected siblings. Long-read sequencing (LRS) revealed this translocation causes a ~115 kb telomeric insertion, shortening the (TTAGGG)_n sequence from ~3 kb to < 1 kb. Methylation-aware analysis showed focal hypomethylation of distal D4Z4 units. Aberrant DUX4 expression was confirmed in fibroblasts from both affected siblings.

We report a novel FSHD mechanism whereby a telomeric translocation causes focal D4Z4 hypomethylation and aberrant DUX4 expression, independent of both repeat contraction and chromatin modifier mutations. Importantly, this mechanism escapes gold-standard diagnostics, underscoring the utility of advanced genomic technologies in genetically unsolved case where clinical suspicion of FSHD is high.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract Cod. 143509

UNRAVELING PHENOTYPIC HETEROGENEITY

IN FSHD THROUGH MACHINE LEARNING-BASED ANALYSIS OF GENOME VARIANTS

Pini S.^{*1}, Angiulli V.³, Pfeifer A.², Suwalska A.², La Vella G.¹, Nuredini A.¹, Albano N.¹, Zoppi D.⁴, Mika J.², Tobiasz J.², Russo A.⁴, Polanska J.², Ruggiero L.⁴, Fosso B.³, Tupler R.¹

¹ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, ² Department of Data Science and Engineering, Silesian University of Technology, Gliwice, Poland, ³ Department of Biosciences, Biotechnology and Environment, University of Bari "A. Moro", Bari, Italy, ⁴ Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples "Federico II", Napoli, Italy

Facioscapulohumeral muscular dystrophy (FSHD) is a hereditary myopathy characterized by marked clinical variability despite a well-defined genetic trigger: loss of epigenetic silencing at 4q35 due to heterozygous contraction of D4Z4 repeats (DRA). The classic Mendelian model fails to explain incomplete penetrance and substantial phenotypic variability observed within FSHD families. This genotype-phenotype gap significantly limits prognostic accuracy, complicates genetic counseling, and hampers patient stratification for clinical trials.

We hypothesize that genetic modifiers across the genome contribute to FSHD clinical heterogeneity. Our study integrates whole-genome sequencing with comprehensive phenotypic characterization and machine learning approaches to identify genetic determinants of disease penetrance and severity.

We analyzed whole-genome sequencing data from 252 DRA carriers across 58 multigenerational FSHD families exhibiting reduced penetrance and variable expressivity. We developed family-aware machine learning pipelines integrating common and rare variant data with deep clinical phenotyping. Different data filtration pipelines and ML models were applied. Our optimal ML model demonstrated robust discrimination between affected and asymptomatic DRA carriers, with potential implications for individual risk prediction. Preliminary analyses identified candidate modifier loci enriched in pathways related to skeletal muscle homeostasis.

This comprehensive genomic approach points at genome-wide genetic variation contributing to FSHD clinical heterogeneity beyond the primary 4q35 locus. The identification of modifier genes and pathways is a critical step toward precision medicine in FSHD. This approach will foster the discovery of novel molecular biomarkers with direct applications in prognostic counseling, clinical trial design, and the development of targeted therapeutic strategies.

WEDNESDAY, MAY 13TH, 2026

16:30-18:00

ORAL COMMUNICATIONS SESSION N. 3

Modular Parallel Room 1-2

Chairs: Caterina Garone, Chiara Pisciotta

GENETIC NEUROPATHIES

Abstract Cod. 143090

HETEROZYGOUS TUBB3 VARIANTS CAUSE ISOLATED OR COMPLEX, AXONAL OR INTERMEDIATE CHARCOT-MARIE-TOOTH DISEASE

Alessandro B.^{*1}, Facchini S.², Van De Vondel L.³, Quartesan I.², Alves G.², Pizzuto F.², Curro R.², Vegezzi E.⁴, Saveri P.¹, Crivellari L.¹, Magri S.⁵, Balistreri F.⁵, Grider T.⁶, Lee Y.⁷, Thomas F.P.⁸, Manji H.², Laura M.², Houlden H.², Shy M.⁶, Zuchner S.³, Reilly M.M.², Pareyson D.¹, Pisciotta C.¹, Cortese A.¹

¹ Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ³ Department of Human Genetics, University of Miami, Miami, United States of America, ⁴ IRCCS Mondino Foundation, Pavia, Italy, ⁵ Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ⁶ Department of Neurology, University of Iowa Heath Care, Iowa City, Iowa, United States of America, ⁷ Department of Neurology, Taipei Veterans General Hospital, Taipei, Taiwan, ⁸ Department of Neurology, Hackensack Meridian School of Medicine & Hackensack University Medical Center, Hackensack, NJ, United States of America

Variants in neuronal β -tubulin III (TUBB3) cause a spectrum of neurodevelopmental disorders, including congenital fibrosis of extraocular muscles and cortical malformations associated with epilepsy with or without peripheral neuropathy, while isolated neuropathy (CMT) due to TUBB3 variants is very rare. We report 15 individuals from 6 families presenting with either pure CMT or CMT-plus harbouring TUBB3 variants.

WES/WGS data from CMT cohorts from Italy/UK/USA/International Genesis initiative were screened for TUBB3 variants. Detailed clinical data from patients carrying pathogenic variants or VUS of possible pathogenic significance in TUBB3 were reviewed.

Fifteen patients from six unrelated families diagnosed with CMT carried TUBB3 variants, including the previously reported pathogenic p.Asp417Asn (N = 12, 4 families), p.Glu194Lys (N = 2, 1 family), and p.Arg156Gly (N = 1), all absent in GnomAD. Inheritance was AD in all families except one sporadic case. Mean age at onset was 40.2 $\pm$ 15.3 years (range 15–61), with sensory symptoms as the initial manifestation in 8/10. Disease severity was moderate-to-severe (CMTES 16.5 $\pm$ 5.2). Forty percent required a walking aid

after 14.1 ± 10.3 years from onset, and 40% became wheelchair-dependent after 25.3 ± 2.5 years. Notably, 4/10 patients showed upper-limb-predominant weakness. Thirty percent had pure CMT, while 70% presented additional features, either mild or detected only on investigations, including cerebellar signs ($n = 5/10$), pyramidal signs ($n = 4/10$), mild cognitive impairment ($n = 3/10$), vestibular/cochlear dysfunction ($n = 2/9$), corpus callosum thinning ($n = 2/9$). Eye involvement was rare ($n = 2/10$). NCS showed length-dependent sensory-predominant neuropathy. TUBB3 variants are an under-recognized cause of CMT and should be considered in dominant or sporadic axonal or intermediate CMT, isolated or with mild CNS involvement.

GENETIC NEUROPATHIES

Abstract Cod. 143348

SERUM POLYOLS AS DISEASE BIOMARKERS IN SORD NEUROPATHY

Quartesan L.^{*1}, Negri S.², Dohrn M.F.³, Haddad S.¹, Liu S.¹, Laurini C.⁴, Tozza S.⁵, Rebelo A.⁶, Beijer D.⁷, Raposo J.⁶, Saporta M.⁶, Achenbach P.⁸, Deschauer M.⁹, Cordts I.⁹, Magri S.¹⁰, Saveri P.¹¹, Vegezzi E.¹², Ripellino P.¹³, Gaetano C.², Rojas--Garcia R.¹⁴, Schlotter--Weigel B.¹⁵, Kayserili H.¹⁶, Manganelli F.⁵, Herrmann D.N.¹⁷, Scherer S.S.¹⁸, Moroni I.¹¹, Pisciotto C.¹¹, Previtali S.⁴, Pareyson D.¹¹, Shy M.E.¹⁹, Zuchner S.L.⁶, Sleight J.¹, Reilly M.M.¹, Cortese A.²⁰

¹ Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ² Laboratorio di Epigenetica, Dipartimento Medicina Riabilitativa NeuroMotoria - MeRiNM, Istituti Clinici Scientifici Maugeri IRCCS, Pavia, Italy, ³ Department of Neurology, Medical Faculty, RWTH Aachen University, Aachen, Germany, ⁴ Neuromuscular Repair Unit, Institute of Experimental Neurology (InSpe), Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy, ⁵ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II, Napoli, Italy, ⁶ Dr. John T. Macdonald Foundation, John P. Hussman Institute for Human Genomics, University of Miami, Miami, United States of America, ⁷ Translational Genomics of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany, ⁸ Institute of Neuropathology, Medical Faculty, RWTH Aachen University, Aachen, Germany, ⁹ Department of Neurology, University Hospital rechts der Isar, Technical University Munich, Munich, Germany, ¹⁰ Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ¹¹ Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ¹² IRCCS Mondino Foundation, Pavia, Italy, ¹³ Department of Neurology, Neurocenter of Southern Switzerland EOC, Lugano, Switzerland, ¹⁴ Department of Neurology, Neuromuscular Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, ¹⁵ Friedrich Baur Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany, ¹⁶ Department of Medical Genetics, Koç University School of Medicine (KUSOM), Istanbul, Turkey, ¹⁷ Department of Neurology, University of Rochester, Rochester, United States of America, ¹⁸ Department of Neurology, The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, United States of America, ¹⁹ Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, United States of America, ²⁰ Department of Medical Biotechnology and Translational Medicine, University of Milan, Milano, Italy

Biallelic loss-of-function variants in the sorbitol dehydrogenase (SORD) cause axonal Charcot-Marie-Tooth (CMT) through sorbitol dehydrogenase (SDH) deficiency and consequent sorbitol accumulation. However, SDH's broad substrate specificity suggests other polyols may accumulate and contribute to pathophysiology. Serum polyol profiling may therefore help clarify associations with disease severity, progression, and demographic or genetic factors, and assess their potential as complementary biomarkers.

Serum sorbitol, xylitol, adonitol, and threitol were measured by UPLC-MS/MS in 47 CMT-SORD patients and 43 controls. Clinical, genetic, and demographic data were collected.

Patients (64% male) had mean disease onset at 19 ± 8 years (11-50) and sampling age 43 ± 14 years (17-79). Sorbitol was 79-fold elevated versus controls (13.3 ± 3.1 vs 0.17 ± 0.09 mg/L; $p < 0.001$), xylitol 37-fold (23.3 ± 5.7 vs 0.63 ± 0.20 mg/L; $p < 0.001$), and adonitol 2.7-fold ($p < 0.001$); threitol showed no difference. No differences in polyol levels or disease severity were observed between missense and truncating mutation carriers. Both sorbitol and xylitol showed a steady increase with age: in patients xylitol increased by 0.21 mg/L/year (95%CI 0.10-0.31; $p < 0.001$) and sorbitol by 0.09 mg/L/year (95%CI 0.03-0.15; $p = 0.003$). Males showed a non-significant trend toward higher age-adjusted sorbitol and xylitol levels compared to females. Foot dorsiflexion weakness, used as a proxy for disease severity, was independently associated with xylitol levels ($\beta = -0.11$; $p = 0.008$) and male sex ($p = 0.019$).

Serum sorbitol and xylitol are excellent diagnostic biomarkers for SORD CMT with complete discrimination from controls. Both suggest progressive age-dependent increase and xylitol showed a promising association with motor impairment, suggesting a potential role as severity biomarkers in therapeutic trials.

GENETIC (MYOPATHIES)

Abstract Cod. 143297

A NOVEL 5' UTR CCG EXPANSION IN TBC1D7 CAUSES OCULOPHARYNGODISTAL MYOPATHY

Curro" R.^{*1}, Van De Vondel L.², Facchini S.¹, Xu I.², De Winter J.³, Quartesan I.¹, Monticelli A.³, Alonso--Jimenez A.⁴, De Ridder W.⁴, Roberts M.⁵, Brady S.⁸, Merve A.⁶, Neveling K.⁷, Hoischen A.⁷, De Jonghe P.⁴, Houlden H.¹, Hanna M.G.¹, Bugiardini E.¹, Züchner S.², Baets J.³, Cortese A.¹

¹ Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ² Dr. John T. Macdonald Foundation Department of Human Genetics and John P. Hussman Institute for Human Genomics, University of Miami, Miami, United States of America, ³ Translational Neurosciences, University of Antwerp, Antwerp, Belgium, ⁴ Neuromuscular Reference Centre, Antwerp University Hospital, Antwerp, Belgium, ⁵ Department of Neurology, Salford Royal NHS Foundation Trust, Manchester, United Kingdom, ⁶ Division of Neuropathology, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, United Kingdom, ⁷ Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands, ⁸ Oxford Neuromuscular Centre, Department of Neurology, John Radcliffe Hospital, Oxford, United Kingdom

Oculopharyngodistal myopathy (OPDM) is a rare inherited myopathy characterized by a combination of progressive ocular, bulbar, and dis-

tal limb weakness. Recently, CCG/CGG repeat expansions in the 5' UTR of six different genes have been associated with OPDM. However, a large proportion of OPDM patients remain genetically unsolved. In this study, we identified a CCG repeat expansion in TBC1D7 as a novel cause of OPDM.

A combination of short and long-read sequencing was employed to identify the repeat and to characterise repeat motif and size across large datasets, including the 100,000 Genome Project. Methylation status was assessed by long-read sequencing. TBC1D7 expression was quantified in patients-derived fibroblasts by qPCR. Routine histopathology and p62-staining were performed on muscle biopsies. CCG expansions in the 5' UTR of TBC1D7 were identified in five individuals from three unrelated OPDM families. Median repeat size in affected cases was 130 units (range: 83-264). The unaffected father of one of the probands carried a large repeat expansion (270 units); however, the expanded allele in this individual was fully methylated and silenced. TBC1D7 transcript levels were upregulated in patient-derived fibroblasts and p62-positive intranuclear inclusions were detected on muscle biopsy, suggesting a gain-of-function mechanism. This study broadens the genetic landscape of OPDM and strengthens the link between the CCG/CGG repeat motif and a characteristic pattern of muscle weakness. It also provides further evidence for the role of epigenetic factors as modifiers of disease penetrance. Finally, it underscores the emerging role of non-coding repeat expansions in unsolved neurogenetic and neuromuscular disorders.

GENETIC (MYOPATHIES)

Abstract Cod. 143399

IN VITRO VARIANT SCREENING IMPROVES VARIANT INTERPRETATION IN ACTN2-RELATED MYOPATHIES

Ranta--Aho J.^{*1}, Kaluzewski T.², Jonson P.H.¹, Sarparanta J.¹, Matuszczyk K.³, Kepczynski L.², Orczykowski M.³, Kaluzewski B.³, Gach A.², Savarese M.¹

¹ *Folkhalsan Research Center, Helsinki, Finland*, ² *Polish Mother's Memorial Hospital Research Institute, Department of Genetics, Lodz, Poland*, ³ *GENOS Sp. z o.o., Laboratory of Medical Genetics, R&D Department, Lodz, Poland*

Variants in ACTN2 are a known cause of both hereditary skeletal muscle myopathy and cardiomyopathy. ACTN2 encodes alpha-actinin-2, a structural sarcomeric protein expressed in both skeletal and cardiac muscle. ACTN2-related diseases are rare, they present with significant clinical heterogeneity, and only a limited number of functional studies have been performed to shed light on the molecular disease mechanisms. Thus, clinical variant interpretation is difficult, leaving many patients without a definitive diagnosis. To improve variant interpretation in ACTN2, we screen over 200 mis-sense variants in vitro to assess their effect on the expressed mutant protein.

We found over 30 variants where more than 25% of the cells were classified as containing aggregates (< 9% in wild type cells and ~40% in positive control). These results have already translated into improved variant interpretation, as we found two families carrying

variants resulting in protein aggregates in our screening.

This study not only expands the mutational and phenotypic spectrum of ACTN2-related disorders but also exemplifies the impact of proactive approach functional studies – variant screening performed before the variants are found in patients can greatly accelerate the path to molecular diagnosis in neuromuscular diseases.

GENETIC NEUROPATHIES

Abstract Cod. 142698

GENETIC MODIFIERS IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: A GENOME-WIDE ASSOCIATION STUDY

Vegezzi E.^{*1}, Alves G.M.², Facchini S.², Planté--Bordeneuve V.¹⁰, Wilson M.⁹, Conceicao I.⁸, Todorova A.⁷, Lemos C.⁵, Coelho T.⁶, Anan I.⁴, Obici L.³, Cortese A.², On Behalf Of T.S.G.

¹ *IRCCS Mondino Foundation, Pavia, Italy*, ² *Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom*, ³ *Amyloidosis Research and Treatment Center, Foundation IRCCS Policlinico San Matteo, Pavia, Italy*, ⁴ *Wallenberg Centre for Molecular Medicine, Umeå University, Umeå, Sweden*, ⁵ *IBMC-Institute for Molecular and Cell Biology, i3S-Instituto de Investigação e Inovação em Saúde, Universidade do Porto, 4200-135, Porto, Portugal*, ⁶ *Centro Hospitalar Universitário do Porto, Porto, Portugal*, ⁷ *Genetic and Medico-diagnostic Laboratory "Genica", Sofia, Bulgaria*, ⁸ *Department of Neurology, Department of Neurology ULS de Santa Maria / CAML; Instituto de Fisiologia, FMUL, Lisbon, Portugal*, ⁹ *Department of Neurology, School of Medicine at Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil*, ¹⁰ *Neurology, AP-HP (Assistance Publique-Hôpitaux de Paris), Henri Mondor University Hospital, Créteil, France*

Hereditary transthyretin amyloidosis (ATTRv) shows marked variability in age of onset (AOO) and clinical presentation across populations and within families. This heterogeneity cannot be fully explained by pathogenic TTR variants alone, suggesting the contribution of additional genetic modifiers.

We performed a genome-wide association study (GWAS) to identify genetic factors influencing AOO in ATTRv amyloidosis. ATTRv patients carrying either the p.Val50Met (p.V50M) or non-p.V50M TTR variants were recruited from 45 centers. Genotyping was performed using the Infinium™ Global Clinical Research Array-24 v1.0 (Illumina; ~1.2 million SNPs), customized with approximately 3,000 additional variants. Association analyses were conducted using GCTA v1.94 under a mixed linear model framework.

A total of 3,011 ATTRv patients were enrolled, 79% of whom were symptomatic. The p.V50M variant was present in 58% of cases, while 42% carried other pathogenic TTR variants. The cohort was predominantly male (62%) of Caucasian ancestry (86%), with 77% reporting a positive family history. Median AOO was 60 years (range: 18–89), varying significantly according to TTR variant, family history, and geographic origin.

After quality control, 2,097 samples were retained. GWAS was performed in 1,919 patients (1,226 p.V50M; 693 non-p.V50M), adjusting for ancestry, TTR variant, and family history. A significant association signal was detected at chromosome 18q12.1 near the TTR locus, largely driven by a shared haplotype in early-onset p.V50M

cases of Portuguese ancestry, independent of Country of origin. These preliminary findings support the presence of cis-acting genetic modifiers that may influence TTR or nearby gene expression, contributing to disease onset variability.

GENETIC NEUROPATHIES

Abstract Cod. 143026

BEYOND DISTAL ARTHROGRYPOSIS: REFINING THE PHENOTYPIC LANDSCAPE OF PIEZO2-RELATED DISORDERS

Capece G.^{*1}, Di Feo M.F.², Melnik E.³, Dadali E.³, Markova T.³, Verloes A.⁴, Ruscitti F.⁴, Lévy J.²¹, Natera--De Benito D.⁵, Ortez C.⁵, Nascimiento A.⁵, Estevez--Arias B.⁵, Kurbatov S.⁶, Murtazina A.³, Elkhateeb N.⁷, Elnaggar W.⁸, Faletra F.⁹, Schymick J.¹⁰, Calvert P.¹⁰, Alanay Y.¹¹, Isik E.¹², Yildiz B.¹³, Bakhtiari S.¹⁴, Kruer M.²⁴, Roos A.¹⁵, Kölbel H.¹⁵, Darvish H.¹⁶, Chouery E.¹⁷, Mehawej C.¹⁷, Mégarbané A.¹⁷, Urtizberea J.A.¹⁸, Senghor H.V.¹⁹, Ndiaye M.¹⁹, Rodriguez Cruz P.M.¹⁹, Sharkov A.²², Bello L.²⁰, Pegoraro E.²⁰, Mio C.⁹, Udd B.²³, Savarese M.²

¹ PhD Program in Translation Specialistic Medicine "G.B. Morgagni", Curriculum "Clinical and Translational Neurosciences, University of Padova, Padova, Italy, ² Folkhälsan Research Center, Helsinki, Finland, ³ Research Centre for Medical Genetics, Moscow, Russian Federation, ⁴ Service de Génétique, Hôpital Robert Debré, AP-HP Paris Nord, Paris, France, ⁵ Neuromuscular Unit, Department of Neurology, Hospital Sant Joan de Déu, Barcelona, Spain, ⁶ Research Institute of Experimental Biology and Medicine, Voronezh State Medical University N.N. Burdenko, Voronezh, Russian Federation, ⁷ Department of Clinical Genetics, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom, ⁸ Department of Pediatrics, Pediatric Neurology and Metabolic Medicine Unit, Kasr Al-Ainy School of Medicine, Cairo University, Cairo, Egypt, ⁹ Department of Medicine, University of Udine, Udine, Italy, ¹⁰ Santa Clara Valley Medical Center, San Jose, California, United States of America, ¹¹ Rare Diseases and Orphan Drugs Application and Research Center-ACURARE, Acibadem University, Istanbul, Turkey, ¹² Ege University Faculty of Medicine, Department of Pediatric Genetics, İzmir, Turkey, ¹³ School of Medicine, Acibadem Mehmet Ali Aydınlar University, Istanbul, Turkey, ¹⁴ Barrow Neurological Institute, Phoenix Children's, Phoenix, Arizona, United States of America, ¹⁵ Department of Paediatric Neurology, Center for Neuromuscular Disorders in Children and Adolescents, University Clinic Medicine, Essen, Germany, ¹⁶ Nikagene Genetic Diagnostic Laboratory, Gorgan, Iran, Islamic Republic of, ¹⁷ Department of Human Genetics, Gilbert and Rose-Marie Chagoury School of Medicine, Lebanese American University, Byblos, Lebanon, ¹⁸ Institut de Myologie, Paris, France, ¹⁹ Neurology Department, Centre Hospitalier National Universitaire de Fann, Dakar, Senegal, ²⁰ Department of Neurosciences, DNS, University of Padova, Padova, Italy, ²¹ Genetics Department, Robert Debré University Hospital, AP-HP Paris Nord, Paris, France, ²² Veltischev Research and Clinical Institute for Pediatrics and Pediatric Surgery of the Pirogov Russian National Research Medical University, Moscow, Russian Federation, ²³ Tampere University Hospital, Tampere Neuromuscular Center, Tampere, Finland, ²⁴ Pediatric Movement Disorders Program, Barrow Neurological Institute, Phoenix Children's Hospital, Phoenix, United States of America

Piezo2 channels are mechanosensors expressed in dorsal root ganglia and Merkel cells, crucial for proprioception and touch sensation. Biallelic PIEZO2 variants cause distal arthrogryposis with impaired

proprioception and touch (DAIPT), whereas patients carrying heterozygous pathogenic variants show a phenotypic spectrum including distal arthrogryposis (DA) type 3, 5, and Marden-Walker syndrome. Most patients have been reported as single cases or in small case series. Further reports are required to further refine the clinical characterization. We retrospectively selected patients with genetically confirmed PIEZO2-related disorders from tertiary referral centers, collecting their clinical data through a standardized assessment. Previously published cases were included when more detailed phenotypic data were available.

We identified 42 cases. Twenty-five of them carried monoallelic variants (mean age at diagnosis 11.9 ± 13.4 years), exhibiting a broad phenotypic spectrum ranging from mild to severe forms, with an additional prenatal diagnosis also reported. Sixteen patients carried biallelic pathogenic PIEZO2 variants (mean age at diagnosis 7.2 ± 4.4 years). They typically presented with neonatal hypotonia and respiratory complications at birth. DA was also associated with scoliosis and a variable multisystemic involvement including scoliosis, hip dislocation, and myopathy.

We provide a comprehensive phenotypic characterization of patients with PIEZO2-related disorders. A clear clinical distinction between recessive and dominant forms emerged. In both cases, the clinical manifestations beyond the peripheral nervous system and Merkel cells suggest a broader PIEZO2 tissue expression during early developmental stages. Our report also suggests a common respiratory involvement, emphasizing the need for regular respiratory follow-up in the long-term clinical management.

WEDNESDAY, MAY 13TH, 2026

16:30-18:00

ORAL COMMUNICATIONS SESSION N. 4

Modular Parallel Room 3

Chairs: Chiara La Morgia, Paola Tonin

METABOLIC MYOPATHIES

Abstract Cod. 143487

WEARABLE SENSOR-BASED QUANTITATIVE GAIT ANALYSIS IN METABOLIC MYOPATHIES: A SINGLE-CENTRE EXPERIENCE

Arena I.G.^{*1}, Usbergo C.², Drago S.F.A.², Rodolico C.², Toscano A.³, Musumeci O.²

¹ BIOMORF Department, University of Messina, Messina, Italy, ² Unit of Neurology and Neuromuscular Disorders, Department of Clinical and Experimental Medicine, University of Messina, Italy, Messina, Italy, ³ ERN-NMD Center for Neuromuscular Disorders of Messina, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy

Quantitative gait analysis offers objective measures sensitive to sub-

tle motor alterations often overlooked by standard clinical evaluation. Wearable sensor-based systems have proven to be reliable and practical for assessing spatiotemporal gait parameters and movement quality in research and clinical contexts. This preliminary study aimed to characterize gait patterns in patients with metabolic myopathies (MMs) compared with healthy individuals using the Baiobit wearable motion analysis system.

25 patients with MMs (10 Pompe Disease, 7 Mitochondrial Myopathies, 4 McArdle Disease, 2 MADD, 1 GSDVII, 1 VLCAD) and 20 age-matched healthy controls underwent comprehensive gait analysis using the Baiobit system, a wearable sensor-based motion analysis platform, according to standardized acquisition protocols. Parameters measured included step velocity, cadence, symmetry, propulsion, step length and duration, stance and swing phase percentages, and pelvic kinematics (tilt, obliquity, rotation). Descriptive statistics (mean $\pm$ SD) were calculated.

Patients showed lower gait velocity (1.15 ± 0.25 vs 1.21 ± 0.01 m/s) and cadence (103.5 ± 22.5 vs 134.8 ± 1.3 steps/min). Gait symmetry was mildly reduced ($93 \pm 7\%$ vs $94.3 \pm 5\%$), and propulsion decreased bilaterally (left: 7.2 ± 5 vs 15 ± 1 m/s²; right: 8 ± 7 vs 14.5 ± 0.5 m/s²). Step length tended to be shorter and more variable, with longer step duration (1.04 ± 0.2 vs 0.96 ± 0.03 s). Pelvic motion showed slightly increased tilt and rotation, suggesting compensatory strategies.

Preliminary gait analysis highlights quantifiable alterations in velocity, cadence, symmetry, propulsion, and pelvic motion in MMs patients compared to healthy controls. These findings support the feasibility of detailed gait assessment as an integration tool in evaluation of motor function in patients with MMs.

MITOCHONDRIAL DISORDERS

Abstract Cod. 143314

CLINICAL AND GENOTYPIC SPECTRUM OF TWINKLE-RELATED DISORDERS INSIGHTS FROM A MULTINATIONAL COHORT STUDY

Lopriore P.¹, Ünlütürk Z.², Klopstock T.³, Karaa A.⁴, Rouzier C.⁵, Domínguez González C.⁶, Lamperti C.⁷, Mancuso M.*⁸

¹ Azienda Ospedaliero Universitaria Pisana/Sant'Anna School of Advanced Studies, Pisa, Italy, ² Neurology Clinic, University of Health Sciences Kocaeli Derince Training Hospital, Turkey, Kocaeli, Turkey, ³ Friedrich-Baur-Institute at the Department of Neurology, LMU University Hospital, Ludwig-Maximilians-Universität (LMU) München, Germany, Munich, Germany, ⁴ Massachusetts General Hospital Genetics Division, Harvard Medical School, Boston, MA, USA, Boston, United States of America, ⁵ Service de génétique médicale, Centre de référence des maladies mitochondriales, CHU Nice, Université Côte d'Azur, CNRS, INSERM, ICRAN, Nice, France, Nice, France, ⁶ Servicio de Neurología - Unidad de Neuromuscular - ERN-NMD CIBERER. Instituto de Investigación imas12. Hospital Universitario 12 de Octubre Madrid, Spain, Madrid, Spain, ⁷ Fondazione IRCCS Istituto Neurologico Carlo Besta, Medical Genetics and Neurogenetics Unit, Milan, Italy, Milan, Italy, ⁸ Department of Clinical and Experimental Medicine, Neurological Institute, University of Pisa, Pisa, Italy

Twinkle, encoded by the TWNK gene, is a mitochondrial DNA helicase that unwinds DNA during replication, crucial for mitochondrial func-

tion. Twinkle-related disorders encompass diverse genetic conditions with mitochondrial dysfunction. Despite several described phenotypes, the full clinical and molecular spectrum remains unclear. This study characterizes phenotypic and genotypic variability in multinational patients with Twinkle-related disorders.

A retrospective cohort study included patients from specialized centers in Italy, France, Germany, Spain, Denmark, Hungary, and the United States, establishing the Twinkle-Related Disorders International Consortium for Trial Readiness (TReDIC). Data from medical records included clinical features, age at onset, disease progression, and genotype. Phenotypes were classified as infantile-onset cerebellar ataxia, parkinsonism, primary mitochondrial myopathy, multisystem involvement, asymptomatic carriers, undetermined, or other. Outcomes included phenotype prevalence, symptom chronology, and mutational patterns.

The study analyzed 189 patients (116 females), mean onset 40.3 years; 70.4% were alive at analysis. Primary mitochondrial myopathy was predominant (85.2%). Common features included progressive external ophthalmoplegia (84.7%), skeletal myopathy (55.6%), hearing loss (17.5%), and psychiatric symptoms (15.3%). At onset, 76.8% had neuromuscular symptoms, 19.6% CNS involvement, and 3.6% multi-organ; after > 8 years, proportions shifted to 54.4%, 23.3%, and 23.3%. Seventy-three TWNK variants (16 novel), mostly missense, clustered in critical functional regions.

This multinational cohort clarifies the broad phenotypic spectrum, progression patterns, and clinically relevant mutational hotspots in Twinkle-related disorders. International collaborations like TReDIC are essential to improve understanding and support future clinical trial design in this rare disease context.

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METABOLIC MYOPATHIES

Abstract Cod. 143440

REAL WORD DATA ON ALGLUCOSIDASE - CIPAGLUCOSIDASE/MIGLUSTAT SWITCHING IN LOPD: AN ITALIAN MULTICENTER EXPERIENCE

Musumeci O.*¹, Arena I.G.¹, Sancricca C.², Servidei S.², Sechi A.³, Filosto M.⁴, Risi B.⁴, Vercelli L.⁵, Mongini T.E.⁵, Fecarotta S.⁶, Parenti G.⁶, Ruggiero L.⁶, Brighina F.⁷, Crescimanno G.⁷, Toscano A.¹

¹ University of Messina, Messina, Italy, ² Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ³ University Hospital of Udine, Udine, Italy, ⁴ University of Brescia, Brescia, Italy, ⁵ University of Turin, Turin, Italy, ⁶ University of Naples, Napoli, Italy, ⁷ University of Palermo, Palermo, Italy

The advent of two next-generation enzyme replacement therapies marks a new era in treating patients diagnosed with late-onset Pompe disease. Clinical trials suggest that they may be better than alglucosidase alfa but real-world data remain limited for the combined therapy cipaglucosidase plus miglustat (cipa-mig).

Herein, we present real-life clinical outcomes in a cohort of 14 LOPD

patients treated with cipamig. We performed a longitudinal analysis of motor and respiratory functions in 14 LOPD patients followed at Italian Neuromuscular expert Centers, who received cipa-mig for at least one year. Parameters assessed included six-minute walking test (6MWT) and forced vital capacity (FVC), GSGC, rPACT and PDIS and PDSS scales collected one year before switching (T-1); at switching (To), after one year (T+1) and at last evaluation (Tlast). The cohort mean age was 50.5 years (range 31–73) and included nine males and five females. 12/14 patients were ERT-experienced, whereas two was ERT-naïve. First generation ERT duration was 8.1 years (range from 2 to 17 years). The follow-up duration under second-generation range from 1–6 years. All patient where ambulant and the mean 6MWT at T0 was 373,7 m $\pm$ 133 m. At last examination 12/14 improved on 6MWD. Regarding respiratory function, the mean baseline of sitting predicted FVC % was 78.5 and at last examination after switching patients showed a stabilization. Most of the patients stabilized or improved in at least one functional parameter. Although individual-level effects were variable, starting or switching to a second-generation ERT may positively influence disease trajectories in LOPD.

MITOCHONDRIAL DISORDERS

Abstract Cod. 143093

BRAIN PHYSIOLOGICAL TRANSCRIPTOMIC ARCHITECTURE UNDERPINNINGS OF REGIONAL VULNERABILITY TO STROKE-LIKE LESIONS IN MELAS

Azzimonti M.^{*1}, Magri F.¹, Piga D.², Del Vecchio G.³, Stroppi M.⁴, Giorgio C.³, Corti S.², Ronchi D.¹, Comi G.P.¹

¹ Neurology Unit, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ² Neuromuscular and Rare Diseases Unit, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ³ Neuroradiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ⁴ Medical Physics Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

Stroke-like lesions (SLLs) in mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) show a non-random regional brain distribution, but the biological basis of this selective vulnerability remains unclear. We used a brain-wide transcriptomic–neuroimaging approach to investigate the relationship between regional gene expression and lesion susceptibility.

Six patients with MELAS due to m.3243A > G mutations and at least one MRI acquired during the acute phase of a stroke-like episode were included. Acute SLLs were segmented on FLAIR images and averaged across patients to generate a lesion probability map (LPM). Spatial correlations between the LPM and the expression of 2,802 energy-metabolism-related genes were assessed using the Allen Human Brain Atlas and the MENGA platform ($p < 0.001$, $R^2 \geq 0.15$). Cell-type-specific expression patterns were explored using the Darnis human brain transcriptome database.

Thirteen MRI scans from distinct stroke-like episodes were analysed. The LPM revealed preferential involvement of occipital, parietal and temporo-polar regions. Higher lesion probability correlated with in-

creased expression of SLBP ($R^2 = 0.725$, $p < 0.001$), linked to histone mRNA processing and cellular replication. Increased expression of genes involved in neurovascular unit regulation, including SGCG ($R^2 = 0.667$, $p < 0.001$) and POSTN ($R^2 = 0.628$, $p < 0.001$), was associated with higher lesion probability. Conversely, lower expression of TMEM127 ($R^2 = 0.617$, $p < 0.001$), a negative regulator of mTOR and HIF- α signaling, characterized more vulnerable regions, implicating impaired metabolic and hypoxic stress responses. In MELAS, SLLs preferentially affect brain regions with higher metabolic demand, greater reliance on neurovascular integrity, and reduced adaptive responses to hypoxia. This imaging–transcriptomic framework helps identify molecular mechanisms underlying stroke-like episodes and potential therapeutic targets.

METABOLIC MYOPATHIES

Abstract Cod. 143469

SWITCHING FROM ALGLUCOSIDASE ALFA TO AVALGLUCOSIDASE: REAL-WORLD DATA FROM A SINGLE-CENTER EXPERIENCE

Musumeci O.^{*}, Arena I.G., Drago S.F.A., Usbergo C., Rodolico C., Toscano A.

University of Messina, Messina, Italy

Second-generation enzyme replacement therapies (ERTs) are now available in clinical practice for the treatment of Late-Onset Pompe Disease (LOPD). Most data about their efficacy and safety came from clinical trials, while long term data on real word settings are still limited. Herein, we present real-life clinical outcomes in a cohort of eight LOPD patients treated with avalglucosidase.

We performed a longitudinal analysis of motor and respiratory functions in 11 LOPD patients followed at the Unit of Neuromuscular disorders of Messina, who received avalglucosidase for at least one year. Parameters assessed included six-minute walking test (6MWT) and forced vital capacity (FVC), which were measured at baseline (corresponding to the start of second-generation ERT) and every 12 months

The cohort mean age was 61.3 years (range 13–82) and included five males and three females. 10/11 patients were ERT-experienced, whereas one was ERT-naïve. All received avalglucosidase-alfa. The mean follow-up duration under second-generation ERT was 3.5 years (range 1–8 years). The mean 6MWT at baseline was 355 m, increasing to 370.5 m at the last follow-up. Regarding respiratory function, the mean baseline FVC% was 68.5%, increasing to 73.8% at the last follow-up, with a mean change of +5.3%. Individual patient trajectories showed that 10/11 patients stabilized or improved in at least one functional parameter

Notably, ERT-naïve pt had stable motor and respiratory function over eight years with avalglucosidase-alfa. 5/11 patients showed improvement in both outcome measures. Longer follow-up in larger cohort is warranted to confirm this positive trend.

OTHERS

Abstract Cod. 143364**RITUXIMAB IN IDIOPATHIC INFLAMMATORY MYOPATHIES: AN ITALIAN MULTICENTER STUDY FROM THE INFLAMMATORY MYOPATHIES AIM STUDY GROUP**

Lucchini M.^{*1}, Bosco L.², Urbano G.⁴, Faedo E.⁹, Velardo D.⁵, Valentino M.L.⁸, Lauletta A.⁷, Carlomagno V.¹, Innocenti F.D.¹, Torchia E.¹, Previtali S.², Laurini C.³, Attolini G.³, Mongini T.E.⁴, Vercelli L.⁴, Grandis M.⁹, Benvenuto G.⁹, Parisi M.⁶, Garibaldi M.⁷, Mirabella M.¹

¹ Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy, ² Ospedale San Raffaele, Milano, Italy, ³ Università Vita Salute San Raffaele, Milano, Italy, ⁴ Neuromuscular Unit, University of Turin, Department of Neuroscience "Rita Levi Montalcini", Torino, Italy, ⁵ Neuromuscular and Rare Disease Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ⁶ Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ⁷ Department of Neuroscience, Mental Health and Sensory Organs-NESMOS Sapienza University of Rome Sant'Andrea Hospital, Roma, Italy, ⁸ Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ⁹ IRCCS Ospedale Policlinico San Martino, Genova, Italy

Although generally responsive to steroids, most patients with Idiopathic Inflammatory Myopathies (IIM) require long-term immunosuppressive treatment to minimize corticosteroid exposure and prevent disease relapses. The efficacy of rituximab has been investigated in the RIM trial, and rituximab is currently reserved for refractory IIM. To evaluate the effectiveness of rituximab in patients with refractory IIM in a national, multicenter cohort. Clinical efficacy was assessed through changes in clinical scores (MMT8), laboratory parameters (CPK levels), and reductions in steroid dosage.

A total of 52 patients from 7 neuromuscular centers were included.

At rituximab initiation, the mean age was 53 years, with a mean disease duration of 48 months and a prednisone-equivalent dose of daily 32.5 mg. The median number of prior treatments was 3, while 30 patients were positive for myositis-specific antibodies. Following rituximab therapy, the mean MMT8 score improved significantly from 124.8 at baseline to 139.6 at 12 months, with changes evident as early as 3 months. Also, CPK levels significantly decreased from 2064 to 634 U/L within the first 3 months. A clinical or laboratory significant improvement was observed in 37 patients. Among those receiving > 20 mg daily prednisone, steroids were tapered in 29/32 cases below 10 mg.

Our study supports rituximab as an effective therapeutic option for patients with refractory IIM, also enabling substantial steroid-sparing effects. Despite the high overall response rate, a subgroup of patients did not achieve optimal improvement, highlighting the need for further therapeutic refinement.

WEDNESDAY, MAY 13TH, 2026

18:45-20:00

ORAL COMMUNICATIONS SESSION N. 5

Modular Parallel Room 3

Chairs: Emanuele D'Amico, Carlo Minetti

MUSCULAR DYSTROPHIES

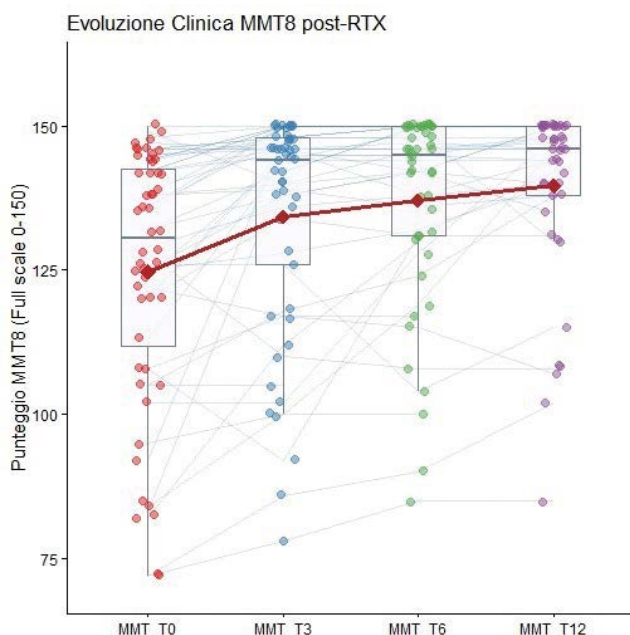
ABSTRACT Cod. 143164

EMERGING ROLE OF MUSCLE- AND FIBROSIS-RELATED MICRORNAS IN EMERY-DREIFUSS MUSCULAR DYSTROPHIES

Farinazzo G.^{*1}, Malacarne C.¹, Tarasco M.C.¹, Mattioli E.², Schena E.², Ricci G.³, Vercelli L.⁴, Ruggiero L.⁵, Carboni N.⁶, Siciliano G.³, Mongini T.E.⁴, Politano L.⁷, Maggi L.¹, Cavalcante P.¹, Marcuzzo S.¹, Lattanzi G.², Bonanno S.¹

¹ Neuroimmunology and Neuromuscular Disease Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ² CNR Institute of Molecular Genetics "L.L. Cavalli-Sforza" Unit of Bologna, Bologna, Italy, ³ Department of Clinical and Experimental Medicine, Neurological Clinic, Pisa, Italy, ⁴ Department of Neurosciences "Rita Levi Montalcini", University of Turin, Torino, Italy, ⁵ Department of Neurosciences and Reproductive and Odontostomalgic Sciences, University Federico II, Napoli, Italy, ⁶ Neurology Department, Hospital San Francesco di Nuoro, Nuoro, Italy, ⁷ Cardiomyology and Medical Genetics, University of Campania Luigi Vanvitelli, Napoli, Italy

The clinical and pathogenic heterogeneity of Emery–Dreifuss muscular dystrophies (EDMDs), ranging from severe childhood-onset to slowly progressive adult forms, hampers early diagnosis and prognostic stratification, highlighting the need for reliable indicators of



disease severity to support early clinical management. Cardiac and skeletal muscles are enriched in specific microRNAs (miRNAs), known as myomiRs (miR-1, miR-133a, miR-133b, miR-206), which play key role in myogenesis and muscle homeostasis by regulating genes involved in muscle atrophy. Additional miRNAs, including miR-100, miR-192, and miR-335, are implicated in myoblast proliferation and differentiation, while others such as miR-34a, -34b, -34c, miR-21, -29 and -96 are associated with fibrotic and senescence-related processes.

Here, we investigated for the first time the involvement of muscle- and fibrosis-related miRNAs and their potential clinical relevance in EDMD. Serum miRNA expression levels were analysed in 32 adult EDMD2 patients and age-matched healthy controls (HC) using TaqMan real-time PCR.

EDMD2 patients showed a significant up-regulation of miR-206, miR-133a, miR-133b, miR-335 ($p < 0.0001$) and miR-100 ($p < 0.001$), suggesting a compensatory miRNA-mediated muscle remodelling response. In parallel, increased levels of miR-29c ($p < 0.0001$), miR-34a and miR-96 ($p < 0.01$), and miR-34c ($p < 0.05$) may reflect key pro-fibrotic disease-related processes. Receiver operating characteristic curve analysis demonstrated good diagnostic performance ($AUC > 0.70$) for the differentially expressed miRNAs.

Overall, our findings identify a panel of miRNAs implicated in EDMD pathogenesis, supporting their potential use as biomarkers and therapeutic targets to improve disease management.

CHILDHOOD NEUROPATHIES

Abstract Cod. 143246

SERUM LIGHT CHAIN NEUROFILAMENTS AS A BIOMARKER IN VINCRISTINE-INDUCED PERIPHERAL NEUROPATHY IN PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

Gotti G.^{*1}, Kullmann G.A.², Zoia C.P.³, Tassistro E.⁴, Gerosa G.⁵, Rinaldi A.⁵, Fantoni F.⁵, Ravizza S.⁵, Bettini L.R.¹, Colombini A.¹, Sala A.¹, Leoni V.¹, Spinelli M.¹, Bungaro S.⁶, Valsecchi M.G.⁵, Balduzzi A.C.⁵, Rizzari C.¹, Cavaletti G.³

¹ Pediatric Hematology-Oncology Unit, Department of Pediatrics, Foundation IRCCS San Gerardo dei Tintori, Monza, Italy, Monza, Italy, ² Child Neuropsychiatry, Foundation IRCCS San Gerardo dei Tintori, Monza, Italy, Monza, Italy, ³ Experimental Neurology Unit and Neurobiology Laboratory, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy, Monza, Italy, ⁴ Biostatistics and Clinical Epidemiology, Foundation IRCCS San Gerardo dei Tintori, Monza, Italy, Monza, Italy, ⁵ School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy, Monza, Italy, ⁶ Tettamanti Research Center, Foundation IRCCS San Gerardo dei Tintori, Monza, Italy, Monza, Italy

Vincristine-induced peripheral neuropathy (VIPN) is a frequent complication in children and adolescents treated for acute lymphoblastic leukemia (ALL). No studies have evaluated neurofilament light chain (NfL) levels in relation to detailed neurological assessments in this patient population.

We conducted a prospective study including 30 patients with ALL (aged 1–17 years) treated according to the AIEOP-BFM ALL 2017 protocol. Assessments were performed at diagnosis (T0), after 3

weeks (T1), and after 5 weeks of treatment (T2). At each time point, patients aged ≥ 3 years underwent evaluation using the pediatric-modified Total Neuropathy Scale, and VIPN severity was categorized as mild (score 0–4), moderate (score 5–9), or severe (score ≥ 10). Blood samples were collected concurrently.

At baseline (T0), none of the patients had neuropathy. At T1, moderate neuropathy was observed in 34.8% of patients. By T2, clinically relevant neuropathy was present in 62.5% of patients, classified as moderate in 45.8% and severe in 16.7%. Patients aged ≥ 10 years were more frequently affected than younger patients at both T1 (50% vs 11.1%) and T2 (73.3% vs 44.4%).

No significant differences in median NfL levels were observed between patients with mild and moderate neuropathy at T1 (53.2 vs 45.1 pg/mL) or T2 (120.3 vs 82.5 pg/mL). In contrast, markedly higher NfL levels were detected in patients with severe neuropathy at T2 (median 233.2 pg/mL).

These findings suggest an association between elevated NfL levels and severe VIPN, supporting further investigation of NfL as a potential biomarker for vincristine-induced neurotoxicity in pediatric patients.

CONGENITAL MYOPATHIES

Abstract Cod. 143075

A MULTICENTER STUDY OF CCDC78-RELATED MYOPATHY: CLINICAL AND ULTRASTRUCTURAL INSIGHTS

Lopergolo D.^{*1}, Berti G.¹, Goodwin R.², Michelassi F.³, Risi B.⁴, Grandis M.⁵, Massa R.⁶, Santorelli F.M.⁷, Gallus G.N.¹, Valentino M.L.⁸, Palombo F.⁹, Zoppi D.¹⁰, Ruggiero L.¹⁰, Esposito G.¹⁶, Kawka A.¹¹, Szczaluba K.¹¹, Magri F.¹², Ronchi D.¹³, Corti S.¹⁴, Savarese M.¹⁵, Filosto M.⁴, Malandrini A.¹, De Stefano N.¹

¹ Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, ² Medical College of Wisconsin, Milwaukee, United States of America, ³ Department of Neurology, Columbia University Medical Center, New York, United States of America, ⁴ NeMO-Brescia Clinical Center for Neuromuscular Diseases, University of Brescia, Brescia, Italy, ⁵ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Genoa, Italy, ⁶ Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ⁷ IRCCS Fondazione Stella Maris, Pisa, Italy, ⁸ Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy, ⁹ IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy, ¹⁰ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy, ¹¹ Centre of Excellence for Rare and Undiagnosed Diseases, Medical University of Warsaw, Warsaw, Poland, ¹² Neuromuscular Unit, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ¹³ Department of Pathophysiology and Transplantation, Dino Ferrari Center, University of Milan, Milan, Italy, ¹⁴ Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, ¹⁵ Folkhälsan Research Center, Helsinki, Finland, ¹⁶ Department of Molecular Medicine and Medical Biotechnologies, University of Naples Federico II; CEINGE Advanced Biotechnologies, Naples, Italy

The CCDC78 gene was identified as a candidate gene for autosomal dominant centronuclear myopathy type 4 (Majczenko et al., 2012). Clinical features in the first reported family included neonatal hypotonia, muscle weakness, myalgias, motor impairment, and cogni-

tive involvement. We reported a second family harboring a nonsense CCDC78 variant, providing insights into CCDC78 interactors and its role in skeletal muscle (Lopergolo et al., 2024). To date, no genotype–phenotype correlation studies have been performed, and this ultrarare myopathy remains poorly characterized.

To establish genotype–phenotype correlations, we collected clinical, molecular, and histopathological data from 14 patients carrying CCDC78 point mutations. Patients were recruited from nine neuromuscular centers in Italy, Finland, Poland, and the United States.

We identified 11 families harboring ten different likely pathogenic germline CCDC78 variants. Age at symptom onset was highly variable. Recurrent clinical features included dropped head syndrome, bilateral scapular winging, and calf hypertrophy. Common histopathological findings on light microscopy were increased internal nuclei, predominance of type I fibers, and core-like areas. Transmission electron microscopy revealed sarcoplasmic reticulum dilatation and mitochondrial abnormalities in several patients. Additional extramuscular findings included atrial structural defects and osteoarticular abnormalities.

This study represents the first comprehensive cohort of patients with CCDC78 mutations and significantly expands the clinical and pathological spectrum of CCDC78-related centronuclear myopathy. Our data provide robust support for the pathogenicity of germline CCDC78 variants. Despite marked phenotypic variability, consistent sarcoplasmic reticulum abnormalities on electron microscopy emerge as a potential disease hallmark, offering a valuable diagnostic clue in patients with congenital unresolved neuromuscular disorders.

ADVANCED DIAGNOSTICS

Abstract Cod. 143446

IMPROVING MOLECULAR RESOLUTION IN NEUROMUSCULAR DISORDERS WITH LONG-READ SEQUENCING

Di Letto P.¹, Russo M.², Romano F.², Iffat Rahman S.², Piluso G.², Torella A.², Nigro V.²

¹ Telethon Institute of Genetics and Medicine, Pozzuoli, Naples, Italy, ² Department of Precision Medicine, University of Campania “Luigi Vanvitelli”, Napoli, Italy

Next-generation sequencing (NGS) has markedly improved the diagnosis of neuromuscular disorders (NMDs). However, many cases remain unsolved or only partially characterised due to intrinsic technical limitations. Short-read exome/genome sequencing is constrained by read length, limiting the detection of repeat expansions, structural variants, and highly homologous regions. As a result, some NMDs cannot be diagnosed at all (e.g. FSHD), while others are incompletely diagnosed, including DM1, DM2, SMA, and DMD, with implications in clinical management and access to targeted therapies.

Since most patients have already undergone short-read sequencing, we developed a cost-effective complementary strategy to address unresolved NMD cases without duplicating existing analyses. Using Oxford Nanopore long-read sequencing combined with Adaptive Sampling, we designed a targeted panel focusing on genomic regions known to harbour NMD pathogenic variants poorly detected

by conventional NGS.

Our design targets 273 neuromuscular genes, including SMN1/2, DMD, DMPK, C9orf72, and DUX4, enhancing the diagnostic power of pre-existing NGS data. In a preliminary study, the panel achieved a mean coverage of ~130×, enabling phasing and high-resolution variant detection across complex loci. Long reads allowed accurate discrimination of duplicated genes and unambiguous identification of repeat expansions. We successfully used this approach in a SMA case identifying a pathogenic SMN1 deletion in trans with a nonsense variant. Additionally, we precisely assessed carrier status for Friedreich ataxia, overcoming the intrinsic limitations of short-read. This targeted long-read approach improves the analytical workflow in NMDs while reducing costs and turnaround time, representing an effective tool for accurate diagnosis and therapeutic address.

OTHERS

Abstract Cod. 143009

TARGETED NGS NEWBORN SCREENING IN EUROPE: FIRST RESULTS FROM THE SCREEN4CARE TREAT PANEL

Selvatici R.^{*1}, Mietto M.², Fortunato F.², Matalonga L.³, Einhorn M.⁴, Rufino B.⁴, Macari G.⁵, Caforio L.⁵, Zuccolo M.⁶, Martinez--Fresno M.⁷, Freyler K.⁸, Davoine E.⁹, Faivre L.⁹, Gut I.³, Agolini E.¹⁰, Novelli A.¹⁰, Bertini E.¹⁰, Sansen S.¹¹, Kirschner J.⁸, Beltran S.³, Ferlini A.²

¹ Università degli Studi di Ferrara, and Consorzio Futuro in Ricerca (CFR), Ferrara, Italy, ² Università degli Studi di Ferrara, Ferrara, Italy, ³ Centro Nacional de Análisis Genómico (CNAG), Barcelona, Spain, ⁴ GENOOX, Amsterdam, Netherlands, ⁵ GenomeUP, Rome, Italy, ⁶ Roche, Basel, Switzerland, ⁷ Illumina, Madrid, Spain, ⁸ Universitätsklinikum Freiburg, Freiburg, Germany, ⁹ CHU Dijon Bourgogne, Dijon, France, ¹⁰ Ospedale Pediatrico Bambino Gesù (OPBG), Rome, Italy, ¹¹ Sanofi, Brussels, Belgium

Screen4Care (ClinicTrials.gov, NCT06549218) will screen 18.000 newborn in Europe by TREAT panel (245 genes). Recruitment began December 2024 in Italy, Germany, France, and Greece, Poland and Czech Republik will join soon. Samples are collected by heel prick on a dried blood spot card and centralized at OPBG for sequencing. Complete enrollment of 18,000 babies by December 2026.

6,433 newborns were enrolled across birth centers and sequencing completed in 4,664 newborns, data processing used two independent bioinformatics pipelines implementing automated variant filtering and prioritization. Overall, 451 newborns (9.6%) were classified as screen-positive and required in-depth downstream interpretation by reference centers to ensure consistent and reproducible variant classification. Variant interpretation included inheritance pattern assessment, review of allele frequencies and updated annotations from reference databases, analysis of aminoacid substitutions and predicted protein impact, identification of mutational hotspots, splicing prediction, and protein domain analysis. Literature revision was also performed for variants in genes with dual inheritance patterns (AD/AR). The Ferrara reference center has managed 297 positive cases among 2,916 enrolled newborns from Emilia Romagna (2230), and France (686). The Rome reference center enrolled 1,084 newborns

and managed 99 positive cases, while the German reference centers enrolled 666 newborns and managed 55 positive cases originating from Freiburg (488), Göttingen (112), and Berlin (66).

Variants curation is still in progress and seems to highlight a quite high true positivity of about 8,5%. Screen4Care project will help in understanding the real frequency of many rare diseases in the EU studied population to design future newborn screening programs.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Abstract Cod. 143006

SYNTHETIC DATA FOR RESEARCH IN CIDP: VALIDATION AGAINST REAL-WORLD DATA FROM THE ITALIAN CIDP REGISTRY

Signori A.¹, Schirinzi E.², Manganelli F.³, Cocito D.⁴, Falzone Y.⁵, Briani C.⁶, Mazzeo A.⁷, Schenone A.¹, Di Stefano V.⁸, Cosentino G.⁹, Marfia G.A.¹⁰, Benedetti L.¹¹, Carpo M.¹², Filosto M.¹³, Leonardi L.¹⁴, Luigetti M.¹⁵, Mata S.¹⁶, Piscosquito G.¹⁷, Rosso T.¹⁸, Lucchetta M.¹⁹, Siciliano G.², Lauria Pinter G.²⁰, Inghilleri M.²¹, Cantisani T.²², Notturmo F.²³, Ricciardi D.²⁴, Habetswallner F.²⁴, Vegezzi E.⁹, De Lorenzo A.²⁵, Lozi C.²⁵, Salvalaggio A.⁶, Strano C.⁵, Gentile L.⁷, Mataluni G.¹⁰, Brighina F.⁸, Risi B.¹³, Poli L.¹³, Forcina F.¹⁴, Moret F.²¹, Canale F.³, Cassano E.²⁶, Dalla Bella E.²⁰, Nobile--Orazio E.²⁵, Doneddu P.E.*25

¹ University of Genova, Genova, Italy, ² University of Pisa, Pisa, Italy, ³ University of Naples Federico II, Napoli, Italy, ⁴ University of Torino, Torino, Italy, ⁵ San Raffaele Scientific Institute, Milano, Italy, ⁶ University of Padova, Padova, Italy, ⁷ University of Messina, Messina, Italy, ⁸ University of Palermo, Palermo, Italy, ⁹ University of Pavia, Pavia, Italy, ¹⁰ Tor Vergata University of Rome, Roma, Italy, ¹¹ IRCCS Ospedale Policlinico San Martino, Genova, Italy, ¹² ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy, ¹³ University of Brescia, Brescia, Italy, ¹⁴ Sant'Andrea Hospital, Roma, Italy, ¹⁵ Università Cattolica del Sacro Cuore, Roma, Italy, ¹⁶ Azienda Ospedaliero-Universitaria di Careggi, Firenze, Italy, ¹⁷ University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno, Italy, ¹⁸ Ospedale San Bassano, Vicenza, Italy, ¹⁹ Ospedale Santa Maria della Misericordia, Rovigo, Italy, ²⁰ IRCCS Foundation 'Carlo Besta' Neurological Institute, Milano, Italy, ²¹ Sapienza University of Rome, Roma, Italy, ²² Azienda Ospedaliera di Perugia, Perugia, Italy, ²³ Ospedale SS di Pescara, Pescara, Italy, ²⁴ Cardarelli Hospital, Napoli, Italy, ²⁵ IRCCS Humanitas Research Hospital, Milano, Italy, ²⁶ Ospedale del Mare, ASL Napoli 1 Centro, Napoli, Italy

Research in CIDP is challenged by the rarity of the disease, limited data sharing, and privacy constraints. Disease registries help address these issues, but reuse of individual-level data remains difficult. Artificial intelligence-generated synthetic data (SD) may offer a privacy-preserving alternative, provided that analytical validity is preserved. To evaluate SD derived from the Italian CIDP Registry using a previously published case-control study as a reference. We analyzed a matched dataset of 195 CIDP cases and 195 controls originally used to study lifestyle and dietary factors. SD were generated using sequential conditional modeling, stratified by sex to preserve the original matching structure. Fidelity was assessed by comparing real and SD in terms of marginal distributions (information-theoretic distances and goodness-of-fit statistics), data distinguishability (propensity score mean squared error), and preservation of associations

with CIDP risk using univariable and multivariable logistic regression. The synthetic dataset preserved the original case-control balance and sex distribution. Categorical variables distributions showed high agreement between real and SD, with minimal smoothing limited to a few multi-level dietary variables. Distinguishability analyses indicated low separability between real and synthetic records. Univariable associations with CIDP risk were well replicated, including protective associations with higher fish and rice intake. Multivariable models showed highly concordant effect estimates between real and SD. Synthetic data generated from the Italian CIDP Registry reliably reproduce key analytical properties of real-world data while preserving patient privacy. This approach supports reproducible and shareable CIDP research and may facilitate future collaborative studies.

THURSDAY, MAY 14TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N. 6

Plenary Room Europa

Chairs: Angelo Antonini, Renato Mantegazza, Rita Rinaldi

MYASTHENIA

Abstract Cod. 143441

CLINICAL RESPONSE HETEROGENEITY TO FIRST-LINE BIOLOGIC THERAPIES IN ACHR-POSITIVE MYASTHENIA GRAVIS

Vanoli F.*¹, Crisafulli S.¹, Habetswallner F.², Erra C.², Di Stefano V.³, Rini N.³, Fionda L.⁴, Rossini E.⁴, Bonanno S.¹, Rodolico C.⁵, Biasini F.⁵, Frangiamore R.¹, Bisecco A.⁶, D'Alvano G.⁶, Iorio R.⁷, Falso S.⁷, Marini S.⁷, Maestri Tassoni M.⁸, Guida M.⁸, Cheli M.¹, Massa R.⁹, Greco G.⁹, Vinciguerra C.¹⁰, Damato V.¹¹, Grandis M.¹², Falzone Y.¹³, Antozzi C.¹, Maggi L.¹

¹ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² UOC Neurophysiopathology, AORN Cardarelli, Via Antonio Cardarelli 9, Naples, Italy, ³ Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy, ⁴ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ⁵ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ⁶ Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Naples, Italy, ⁷ Neurology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ⁸ Neurology Unit, Department of Neurosciences, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy, ⁹ Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ¹⁰ Neurology Unit, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy, ¹¹ Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, ¹² Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics and Maternal Infantile Sciences, University

of Genoa, Genoa, Italy, ¹³ Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy

The recent introduction of biologic therapies reshaped the treatment paradigm of AChR-positive myasthenia gravis (AChRMG).

In this study, we investigated the clinical characteristics of patients who failed to respond to first-line biologic therapies, including efgartigimod, eculizumab, ravulizumab, and zilucoplan.

A total of 289 AChRMG patients were included, classified as first-line responders (n = 252) or first-line non-responders (n = 37). No significant differences were observed at baseline between the two groups regarding sex, age at onset, disease duration, thymic involvement, prior or concomitant treatments, or MG-ADL and QMG scores. Likewise, no differences in first-line response rates were observed among biologic agents, except for eculizumab-treated patients, who exhibited higher baseline disease severity and greater prior immunosuppressive exposure, reflecting its use limited to refractory cases.

Although no baseline features reliably predicted non-responsiveness, analysis of responders identified two distinct response phenotypes: short-responders to efgartigimod, defined by the need

for ≥ 5 treatment cycles/year, and partial-responders to complement inhibitors, defined by persistent MG-ADL scores ≥ 6 despite treatment. Short-responders showed a strong female and early-onset predominance ($p < 0.001$), more frequent thymic involvement ($p = 0.038$), and a more refractory disease course. Partial-responders were also predominantly female but were characterized by higher baseline MG-ADL scores ($p = 0.045$) and more frequent use of a single immunosuppressive agent at baseline ($p = 0.017$), suggesting that optimization of conventional immunosuppression may improve outcomes.

Overall, no specific clinical features predicted response to biologic therapies, and first-line efficacy was comparable across agents. Distinct response phenotypes highlight heterogeneity and support a phenotype-oriented approach, underscoring the need for biomarkers to guide treatment strategies.

MYASTHENIA

Abstract Cod. 143484

IMPACT OF TARGETED THERAPIES ON THE DISEASE COURSE OF GENERALIZED MYASTHENIA GRAVIS

Frangiamore R.^{*}, Vanoli F., Cavalcante P., Salvucci G., Giacomuzzi Grigoli E., Marta C., Bonanno S., Maggi L., Antozzi C.
UOC Neurology 4 – Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; Milan, Italy

Targeted therapies (i.e. complement and neonatal Fc receptor inhibitors) have recently expanded the therapeutic scenario for generalized myasthenia gravis (gMG), showing effectiveness and good safety profiles. We evaluated the impact of targeted therapies on clinical parameters, and need for hospitalization and immunomodulation in gMG.

We evaluated in a real-world setting 81 patients with gMG (56 females), mean follow-up 30.4 ± 15.5 months. Treatments included efgartigimod (n = 31), ravulizumab (n = 19), eculizumab (15), ro-zanolixizumab (n = 9) and zilucoplan (n = 7). Clinical assessments were performed longitudinally using MG-ADL, QMG, MGC and MG-QoL15-r. Mean age at baseline was 52.5 ± 15.3 years and mean disease duration was 13.4 ± 12.3 years. 40.7% were considered as treatment-refractory. Mean baseline prednisone dose was 25.6 ± 14.7 mg/day. In the two years preceding prescription of a targeted therapy, 69.1% of patients required plasma exchange or IVIG (mean 4.2 ± 5 cycles), 30.9% were hospitalized due to gMG exacerbations and 4.9% required ICU admission.

During treatment with targeted therapies, patients hospitalized decreased from 30.9% to 2.5%, no ICU admissions occurred. Minimal symptom expression (MSE) was achieved within one month by 45% of patients during Complement inhibition and by 59% during FcRn treatment; mean steroid dose dropped from 25.6 ± 14.7 to 12.2 ± 8.9 mg/day at last follow-up. No major adverse events occurred.

In a real-world setting, targeted therapies reduced the disease burden in terms of hospitalization and immunomodulation requirements, with a steroid-sparing effect and improved quality of life.

MYASTHENIA

Abstract Cod. 143358

FUNCTIONAL CHARACTERIZATION OF ANTIBODIES DIRECTED AGAINST CLUSTERED ACETYLCHOLINE RECEPTOR

Lotti A.¹, Beretta F.¹, Schiavo E.¹, Guida M.², Cepele A.², Erra C.³, D'Alvano G.⁴, Giacomuzzi E.⁵, Rini N.⁶, Rossini E.⁷, Vattemi G.N.⁸, Tonin P.⁸, Sgarzi M.⁹, Alboini P.E.¹¹, Della Cava F.M.¹⁰, Faedo E.¹², Velardo D.¹³, Ginanneschi F.¹⁴, Grandis M.¹², Iovino V.², Iafrate A.¹, Fionda L.¹⁵, Di Stefano V.⁶, Maggi L.⁵, Bisecco A.⁴, Habetswallner F.³, Maestri Tassoni M.², Spagni G.^{*1}, Damato V.¹

¹ NEUROFARBA Department, University of Florence, Firenze, Italy,

² Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ³ Neurophysiopathology Unit, AORN Cardarelli, Napoli, Italy,

⁴ Department of Advanced Medicine and Surgical Sciences, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy, ⁵ Neurology

and Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Neurological Institute Carlo Besta, Milano, Italy, ⁶ Department

of Biomedicine, Neuroscience and advanced Diagnostic, University of Palermo, Palermo, Italy, ⁷ Department of Neuroscience, Mental Health

and Sensory Organs (NESMOS), SAPIENZA University of Rome, Roma, Italy, ⁸ Department of Neurosciences, Biomedicine and Movement

Sciences, Section of Clinical Neurology-University of Verona, Verona, Italy,

⁹ Neurology Unit – Papa Giovanni XXIII Hospital, Bergamo, Italy, ¹⁰ Neurology

Unit – ASL1, Sanremo, Italy, ¹¹ Neurology Unit – IRCCS Casa Sollievo

della Sofferenza Foundation, San Giovanni Rotondo, Italy, ¹² Department

of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal

and Infantile Sciences (DINOEMI) – University of Genoa, Genova, Italy,

¹³ Neuromuscular and Rare Diseases Unit, Department of Neuroscience

– Fondazione IRCCS Ca' Granda; Ospedale Maggiore Policlinico, Milano,

Italy, ¹⁴ Department of Medical, Surgical and Neurosciences – University of

Siena, Siena, Italy, ¹⁵ Neuromuscular and Rare Disease Centre, Neurology

Unit – Sant'Andrea Hospital, Roma, Italy

Antibodies against clustered acetylcholine receptor (AChR), detected by live cell-based assays (CBAs), identify a distinct subgroup of myasthenia gravis (MG), frequently associated with milder disease. However, the pathogenic potential of these antibodies remains incompletely defined. We aimed to characterize their ability to activate complement and induce antigen internalization, and to explore clinical correlates.

Sera from 88 MG patients positive for clustered-AChR antibodies by live-CBA were collected in a multicenter Italian cohort. Complement activation and antigen internalization were assessed in vitro by flow cytometry using HEK-293T cells expressing adult- or fetal-AChR. Complement deposition was quantified by C3/C3b/iC3b staining, while internalization was measured by reduction of α -bungarotoxin binding in stable AChR-expressing cell lines.

Functional pathogenic activity was detected in 23/88 sera (26.1%). Eleven sera induced complement activation alone, four induced antigen internalization alone, and eight showed both mechanisms. Functional effects were observed on both adult- and fetal-AChR and, in a subset, extended beyond the isoform identified by diagnostic CBA. Patients with functionally active antibodies showed a consistent trend toward generalized disease, higher maximum MGFA class, and less favorable post-intervention status, although these differences did not reach statistical significance.

Only a minority of clustered-AChR-positive sera displayed in vitro pathogenic activity, markedly lower than what is reported in classical AChR-MG. This selective and limited functional profile supports the concept that clustered-AChR antibodies define a biologically distinct MG subgroup, characterized by reduced effector mechanisms and a generally milder clinical course. Functional assays may provide complementary information for patient stratification beyond antibody detection alone.

MYASTHENIA

Abstract Cod. 142904

RITUXIMAB IN ACHR AND MUSK MYASTHENIA GRAVIS: LONG-TERM FOLLOW-UP WITH DIFFERENT THERAPEUTIC PROTOCOLS

Tuccillo F.*, Ricciardi D., Erra C., Matrone F., Fasolino A., Della Valle P., Habetswallner F.
UOC Neurofisiopatologia AORN Cardarelli, Napoli, Italy

Myasthenia Gravis is an autoimmune disease caused by specific antibodies targeting the neuromuscular junction.

The objective of our study is to describe a real-world, single-center experience with the long-term efficacy and safety of rituximab therapy in patients with generalized MG. Forty-four patients (AChR n = 22, Musk n = 22) with refractory myasthenia gravis or inadequate disease control were treated with rituximab from January 2009 to May 2025. A subset of anti-Musk MG patients received a low-dose protocol. The primary endpoint was the Myasthenia Gravis Foundation of America post-intervention status success. Secondary endpoints included changes in Myasthenia Gravis activities of daily living over time, responder status, and time to reduced or discontinued steroid therapy.

At 60 months, 33.3% of the AChR and 66.7% of the Musk group achieved success in post-intervention status. Additionally, 76.2% of the AChR group and 90.9% of the Musk group decreased steroid doses, reaching the target of 10 mg/day or less at one year and six months, respectively. Stable steroid discontinuation was possible in 42.9% of the AChR group (median time: 84 months) and 68.2% of the Musk group (median time: 12 months). Within the Musk subgroup, treatment response was consistently higher in the 1000 mg group. However, both dosing strategies resulted in significant clinical improvements, and time-to-event steroid outcomes did not differ substantially by dose. Musk serotype was the only significant predictor of treatment success. This study provides real-world, long-term data on the effectiveness and safety of rituximab in treating generalized myasthenia gravis with either anti-AChR or Musk antibodies.

MYASTHENIA

Abstract Cod. 143350

LATE-ONSET MYASTHENIA GRAVIS: CLINICAL PHENOTYPE AND LONGITUDINAL THERAPEUTIC MANAGEMENT IN A RETROSPECTIVE STUDY

Angelini L.*¹, Arici D.², Laurini C.¹, Sorrenti B.¹, Padovani A.², Filippi M.¹, Previtali S.C.¹, Volonghi I.², Falzone Y.M.¹

¹ IRCCS Ospedale San Raffaele, Neurology department, Milan, Italy,

² Department of Continuity of Care and Frailty, Neurology Unit, ASST-Spedali Civili, Brescia, Italy

Late-onset myasthenia gravis (LOMG) is common, but management data are limited; we aimed to characterize its clinical features and treatment outcomes.

Patients from two referral centers were retrospectively included. Clinical data were collected at disease onset and at 6, 12, and 24 months (T6-T12-T24).

Among a total of 449 MG patients, 54.1% (n = 243) had LOMG; follow-up data were available for 179 patients (73.6%). Mean age at onset was 68.1±10.7 years, male-to-female ratio 1.9:1. MGFA class at onset was I in 20.4%, II in 47.2%, III in 24.1%, IV in 6.5%, and V in 1.8%. Thymoma was present in 11.7%. Antibody status was AChR-positive in 84.5%, seronegative in 14.5%, and MuSK-positive in 1.0%. Mean MG-ADL and QMG scores at onset were 4.2±2.9 and 6.8±4.6, respectively. Minimal manifestation status was achieved in 68.8% at T12 and 64.1% at T24. At T12 and T24 in minimal manifestation patients, treatment included no therapy or pyridostigmine only (26.1%-29.2%), corticosteroid monotherapy (6.9%-10.4%), corticosteroids plus pyridostigmine (26.0%-14.6%), and immunosuppressants (41.1%-45.8%). Corticosteroid withdrawal was achieved in 23.8% after a mean of 12.5 ± 3.2 months. Azathioprine was used in 32.9%, with discontinuation due to adverse events in 11.9%. Among patients with MGFA class I at onset (n = 61), 31.1% developed generalized MG during the 2-year follow-up. Patients with onset > 75 years required lower steroid doses to achieve minimal symptom expression at T24 (p = 0.009).

Late-onset MG accounts for most MG cases; onset after 75 years is associated with a milder course and lower corticosteroid requirements.

MYASTHENIA**Abstract Cod. 143345****COMPARATIVE EFFICACY OF ANTI-C5 VS. ANTI-FCRN THERAPY IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: A MULTICENTRE RETROSPECTIVE STUDY**

Cepele A.*⁸, Maestri Tassoni M.¹, Alboini P.E.², Businaro P.³, Damato V.⁴, Erra C.⁵, Falso S.⁶, Fionda L.⁷, Florio L.², Gastaldi M.³, Habetswallner F.⁵, Iorio R.⁶, Iovino V.¹, Lo Iacono A.¹, Marini S.⁶, Matrone F.⁵, Natoli S.⁹, Pugliese A.⁹, Rossini E.⁷, Rodolico C.⁹, Tufano L.¹⁰, Verza M.U.⁴, Guida M.¹

¹ Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy, ² Neurology Unit, Fondazione IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy, ³ Neuroimmunology Research Section, IRCCS Mondino Foundation, Pavia, Italy, ⁴ Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Firenze, Italy, ⁵ UOC Neurophysiopathology, AORN Cardarelli, Via Antonio Cardarelli 9, Napoli, Italy, ⁶ Department of Neuroscience, Università Cattolica del Sacro Cuore, Roma, Italy, ⁷ Department of Neuroscience, Mental Health and Sensory Organs (NEMOS), SAPIENZA University of Rome, Roma, Italy, ⁸ Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy, ⁹ Unit of Neurology and Neuromuscular Disorders, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ¹⁰ Department of Neuroscience, Mental Health and Sensory Organs (NEMOS), Faculty of Medicine and Psychology,

SAPIENZA University of Rome, Sant'Andrea Hospital, Roma, Italy

Thymoma-associated Myasthenia Gravis (TAMG) represents a challenging clinical phenotype. While anti-complement therapy (C5IT) and neonatal-Fc-receptor inhibitors (aFcRn) have expanded the therapeutic landscape, comparative data regarding their efficacy in TAMG are lacking. This study evaluated the comparative efficacy and corticosteroid (CS)-sparing potential of C5IT versus aFcRn in TAMG patients.

We conducted a retrospective study of 93 AChR-positive TAMG patients (58 C5IT maintenance; 35 aFcRn cycles) across eight Italian centres. The primary endpoint included longitudinal changes in MG-ADL, QMG, daily CS dosage over 12 months. LMM was performed to assess treatment-by-time interactions. aFcRn patients were stratified into "short responders" (mean cycles-intervals < 8 weeks) and "long responders" (mean cycles-intervals ≥ 8 weeks).

Baseline demographics and disease severity were comparable between cohorts. While both groups exhibited clinical improvement, LMM analysis demonstrated a significant treatment-by-time interaction favouring C5IT for MG-ADL ($F = 8.48$, $p = 0.004$) and daily CS reduction ($F = 6.284$, $p = 0.013$). C5IT achieved greater mean reductions in MG-ADL (-6.43 vs. -3.21) and daily CS dosage (-10.8 mg vs. -6.6 mg) compared to aFcRn. Subgroup analysis revealed that aFcRn "short responders" (43% of the cohort) had significantly inferior outcomes compared to both C5IT and aFcRn "long responders". In TAMG patients, chronic C5IT maintenance regimen provides a greater overall clinical improvement and daily corticosteroids com-

Table n.1**Demographic and clinical data gathered at recruitment**

Demographic data Sex, Age at onset, Age at recruitment	
Clinical data before treatment	Thymectomy (yes/no), Date of thymectomy, Months from thymectomy to new therapies, Thymoma classification WHO (A, AB, B1, B2, B3), Thymoma classification Masaoka (I/IIa, IIb, III, IV), AChR titre pre-thymectomy (nmol/l), AChR titre post-thymectomy (nmol/l), AChR titre post-new therapies (nmol/l), Previous therapies (maximum dosage), Previous (IVIg) (yes chronic/yes rescue/no), Previous plasma exchange (PLEX) (yes chronic/yes rescue/no), 1-yr pre-complement inhibitors MG rescue therapy (number and type), Other therapies baseline (type and dosage), chronic IVIg and PLEX baseline* (yes/no).
MG Outcome Measures	MG Activities of Daily Living scale (MG-ADL)**, Quantitative Myasthenia Gravis (QMG)**, 15-item Revised MG Quality of Life scale (MG-QoL-15r [5])**, MGFA at onset, baseline and worst;
Clinical Data during treatment	Steroid dosage (mg) **, Immunosuppressant reduction (type and last follow-up dosage), Immunosuppressant withdrawal (type, date), IVIg (n), PLEX (n), disease relapse (n), crisis (n). Adverse events: side effects (yes/no, type), aFcRn or C5IT withdrawal (yes/no, reason, date).
Clinical data specific for anti-FcRn group	Number of cycles (n), Mean interval between cycles (weeks from end of cycle to new cycle beginning), Cycles number in 1 year (n), Cycles number in 6 months (only for pt with follow up <1y), IgG dosage pre-/post- cycle (g/l)

* Baseline was defined as the evaluation at the last follow up before C5IT or aFcRn therapies start.

** parameters evaluated at different timepoints: baseline, 1, 3, 6, 9, 12 months

pared to aFcRn cycle-based treatment schedule in TAMG patients. aFcRn patients requiring frequent cycling (< 8 weeks) had suboptimal responses, whereas those with sustained durability mirrored C5IT efficacy. These findings highlight the necessity of predictive factors to identify potential “short responders” and optimize personalized treatment selection and administration schedules.

THURSDAY, MAY 14TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N. 7

Modular Parallel Room 1-2

Chairs: Dario Cocito, Matteo Garibaldi

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143444

LIMITATIONS OF STANDARD OF CARE THERAPY IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY

Lozi C.^{*1}, De Lorenzo A.¹, Cocito D.², Fazio R.³, Manganelli F.⁴, Benedetti L.⁵, Filosto M.⁶, Marfia G.A.⁷, Di Stefano V.⁸, Cosentino G.⁹, Gentile L.¹⁰, Luigetti M.¹¹, Siciliano G.¹², Canale F.¹³, Briani C.¹⁴, Piscoquito G.¹⁵, Leonardi L.¹⁶, Rosso T.¹⁷, Ricciardi D.¹⁸, Lauria G.¹⁹, Cavalletti G.²⁰, Cantisani T.²¹, Carpo M.²², Inghilleri M.²³, Falzone Y.³, Spina E.⁴, Cabona C.⁵, Risi B.⁶, Mataluni G.⁷, Vegezzi E.⁹, Mazzeo A.¹⁰, Vitali F.¹¹, Schirinzi E.¹², Salvalaggio A.¹⁴, Nobile--Orazio E.¹, Doneddu P.E.¹

¹ Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, Milan, Italy, ² Department of Neuroscience, University of Turin, Turin, Italy, ³ Division of Neuroscience, Department of Neurology, Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy, ⁴ Department of Neuroscience, Reproductive Sciences, and Odontostomatology, University of Naples “Federico II”, Naples, Italy, ⁵ Neurology Clinic, IRCCS Ospedale Policlinico San Martino Genova, Genoa, Italy, ⁶ Center for Neuromuscular Diseases and Neuropathies, Unit of Neurology, ASST “Spedali Civili”, University of Brescia, Brescia, Italy, ⁷ Dysimmune Neuropathies Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ⁸ Department of Biomedicine, Neuroscience, and Advanced Diagnostics, University of Palermo, Palermo, Italy, ⁹ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, ¹⁰ Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina, Italy, ¹¹ Neurology Department, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, ¹² Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ¹³ Division of Neurology and Neurophysiopathology, Department of Medical and Surgical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy, ¹⁴ Neurology Unit, Department of Neuroscience, University of Padua, Padua, Italy, ¹⁵ Neurology Unit, University of Salerno, Salerno, Italy, ¹⁶ Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs, Faculty of Medicine and Psychology, “Sapienza”

University of Rome, Sant'Andrea Hospital, Rome, Italy, ¹⁷ UOC di Neurologia, Ospedale San Bassano, Vicenza, Vicenza, Italy, ¹⁸ Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy, ¹⁹ Unit of Neuroalgology, IRCCS Foundation “Carlo Besta” Neurological Institute, Milan, Italy, ²⁰ School of Medicine and Surgery and Experimental Neurology Unit, University of Milano-Bicocca, Milan, Italy, ²¹ Servizio di Neurofisiopatologia, Azienda Ospedaliera di Perugia, Perugia, Italy, ²² Department of Neurology, ASST Bergamo Ovest-Ospedale Treviglio, Treviglio, Italy, ²³ Neurodegenerative Diseases Unit, Department of Human Neuroscience, Sapienza University, Policlinico Universitario Umberto I, Rome, Italy

Although standard therapies improve chronic inflammatory demyelinating polyneuropathy (CIDP), efficacy is variable and often requires ongoing treatment to prevent relapse.

This study systematically evaluates these limitations in a large real-life CIDP cohort. Data from the Italian CIDP registry were analyzed in patients on standard-of-care therapy for ≥1 year. Patients were stratified by treatment duration (1–< 3, 3–< 5, > 5 years) and timing (≤1 vs > 1 year from symptom onset). Overall outcomes were residual disability and quality of life under standard therapy, non-responsiveness to ≥1 standard modality, and need for prolonged maintenance to sustain clinical stability. Residual disability was INCAT ≥2 in upper or lower limbs.

Among 555 patients, residual disability affected 51% after one year of therapy and persisted in 51% after two years; 35% had moderate to severe limb disability (INCAT UL ≥3 or LL ≥2, or both). Overall, 72% were unable to perform at least one RODS activity and 56% two or more, mainly running (69%) and prolonged standing (45%), while 21% could not walk more than 1 km. Activity limitations differed between typical CIDP and CIDP variants but not by treatment duration or timing. Among IVIG-treated patients, 137 (76%) were non-responders, while 178 of 352 (50%) failed corticosteroids; only 10% discontinued therapy for at least six months.

Despite prolonged immunomodulatory therapy, more than half of patients had residual disability, often moderate to severe. A minority were unresponsive to first-line therapy, and most required ongoing maintenance to prevent relapse, underscoring the need for more effective and sustained CIDP treatments.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143071

ANTIBODIES AGAINST PROTEOLIPID PROTEIN-1 ARE IDENTIFIED IN PATIENTS WITH INFLAMMATORY NEUROPATHIES

De Lorenzo A.^{*1}, Llarch Cegarra P.², Caballero--Ávila M.², Riesco--Navarro G.², Cortés--Vicente E.², Ana V.², Lleixà C.⁵, Collet--Vidiella R.², Martín--Aguilar L.², Pascual--Goñi E.², Gastaldi M.³, Masciocchi S.³, Querol L.⁴

¹ Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, Milan, Italy, ² Department of Neurology, Neuromuscular Diseases Unit, Hospital de La Santa Creu i Sant Pau, Barcelona, Spain, ³ Neuroimmunology Laboratory and Neuroimmunology Research Section, IRCCS Mondino Foundation, Pavia, Italy, ⁴ Department of Neurology, Neuromuscular Diseases Unit, Hospital de La Santa Creu i Sant Pau and Universitat Autònoma de Barcelona, Barcelona, Spain, ⁵ Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

Conformational antibodies to proteolipid protein-1 (PLP1-IgG), a major myelin protein, have been reported in CNS demyelinating disorders with peripheral involvement, but their prevalence and clinical significance in isolated inflammatory peripheral neuropathies remain unclear.

A validated live cell-based assay for PLP1-IgG detection was implemented. We tested 173 patients with inflammatory neuropathies [94 chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), 72 Guillain-Barré syndrome (GBS), 7 autoimmune nodopathies (AN)] and 48 controls. Clinical data were retrospectively extracted from medical records.

PLP1-IgG were detected in 13/173 (7.5%) inflammatory neuropathy patients and in none of the controls. Seropositivity occurred in 11/94 CIDP (11.7%), 1/72 GBS (1.4%), and 1/7 AN-CNTN1 (14.3%). Among seropositive CIDP patients, six were male (54.5%) and mean age at onset was 53.2±16.4 years. Eight (72.7%) had a typical phenotype and three (27.3%) a multifocal variant; onset was acute/subacute in eight (72.7%). Ataxia occurred in nine (81%), tremor in three (27.3%), and cranial nerve involvement in three (27.3%). Electrophysiology confirmed demyelinating neuropathy in all cases, including conduction block in seven (63.6%); one patient had GM1-IgG. CSF analysis (8 patients) showed albuminocytological dissociation in seven (87.5%; mean protein concentration 104.7±62.9 mg/dL). Treatment response was satisfactory in 7/11 to IVIg (63.6%) and in 5/9 to corticosteroids (55.6%). Two refractory patients improved partially with plasma exchange; one subsequently underwent HSCT with substantial improvement.

PLP1-IgG identify a subset of inflammatory neuropathy patients characterized by frequent acute/subacute onset, ataxia, and generally favorable response to immunomodulatory therapy. Their pathogenic role remains unclear, particularly given co-existing pathogenic antibodies in two cases.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143407

WHEN DEMYELINATION IS NOT DEMYELINATION: RETHINKING NERVE CONDUCTION FINDINGS IN AUTOIMMUNE NODO/PARANODOPATHIES

Cassano E.^{*1}, Doneddu P.E.², Vegezzi E.³, Cosentino G.³, Rugginini B.¹⁰, De Lorenzo A.², Fiumarella R.⁴, Falzone Y.⁵, Castiglia M.⁴, Aiello A.⁴, Canale F.⁴, Gallo C.², Merola G.⁶, Ucci M.⁶, Vitali F.⁷, Bencivenga R.P.⁸, Iovino A.⁸, Fasano C.², Spalletti M.⁹, Matà S.⁹, Ricciardi D.¹², Habetswallner F.¹², Luigetti M.⁷, Previtali S.⁵, Gastaldi M.¹¹, Nobile Orazio E.², Manganelli F.⁴, Tozza S.⁴

¹ Neurology & Stroke Unit, Ospedale del Mare, Naples, Italy, ² Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, Milano, Italy, ³ IRCCS Mondino Foundation, Pavia, Italy, ⁴ Department of Neuroscience and Reproductive and Odontostomatological Sciences, University Federico II, Naples, Italy, ⁵ Neurology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, ⁶ Neurology & Stroke Unit, Moscatti Hospital, Aversa, Italy, ⁷ Department of Neurosciences, University Cattolica del Sacro Cuore, Roma, Italy, ⁸ Neurology and Stroke unit, University Hospital San Giovanni di Dio e Ruggi d'Aragona, Salerno, Italy, ⁹ Neurophysiology

Unit, Neuro-Muscular-Skeletal Department, Careggi Hospital, University of Florence, Florence, Italy, ¹⁰ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, ¹¹ Neuroimmunology Laboratory and Neuroimmunology Research Section, IRCCS Mondino Foundation, Pavia, Italy, ¹² Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy

Autoimmune nodo/paranodopathy (AN) is a subgroup of immune-mediated neuropathies caused by autoantibodies targeting proteins at the node/paranodal regions leading to dysfunction of saltatory conduction rather than demyelinating/remyelinating process as typically occurs in Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). The aim of this study was to evaluate the demyelinating electrophysiological features in AN cohort.

Eighty-nine patients were retrospectively recruited from nine specialized centers. Demographic data, antibody status, and clinical features were collected. The following demyelinating electrophysiological features in upper limb nerves were evaluated: distal motor latency (DML), motor nerve conduction velocity (MNCV), motor nerve conduction blocks (CBs), distal Compound Muscle Action Potential (CMAP) duration, temporal dispersion (TD; proximal-to-distal negative phase CMAP duration ratio > 30%) and presence of multiphasic CMAP (at least 2 baseline crossings).

Twenty-four AN (F/M:4/24; age:57.8±24.3) and 65 CIDP (F/M:20/65; age:57.9±13.2) were recruited. AN patients presented acute/subacute onset, high disability and ataxia. No significant differences were observed for DML, MNCV, CBs and increased distal CMAP duration (23.9% AN vs 13.7% CIDP) between two groups. TD did not differ between groups, and it was abnormal in 19% vs 37% patients (p = 0.17). Moreover, the presence of multiphasic CMAPs were exclusively observed in CIDP group (0% vs 20.6%, p = 0.015).

Classical demyelinating parameters, including TD, do not reliably differentiate AN from CIDP. However, the absence of multiphasic CMAPs in AN may reflect the different underlying pathophysiological mechanism. These findings highlight the limitations of standard electrophysiological criteria in distinguishing AN from CIDP and emphasize the diagnostic value of multiphasic CMAPs.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143353

LONG-TERM OUTCOME IN REFRACTORY ANTI-MAG ANTIBODY NEUROPATHY PATIENTS TREATED WITH BTK INHIBITORS

Tierro B.^{*1}, Visentin A.², Minicuci G.M.¹, Cerantola E.¹, Cacciavillani M.³, Danesin N.², Cellini A.², Angotzi F.², Salvalaggio A.¹, Briani C.¹

¹ Neurology Unit, Department of Neurosciences, University of Padova, Padova, Italy, ² Hematology Unit, Department of Medicine, University of Padova, Padova, Italy, ³ CEMES-EMG Lab, Synlab Group, Padova, Italy

Polyneuropathy with antibody (Ab) against membrane associated glycoprotein (antiMAG NP) carries MYD88 L265P mutation in almost 60% of the patients. This mutation favors the activation of BTK, a key protein stimulating the survival and proliferation of pathogenetic B-cells.

We describe clinical, neurophysiological and hematological param-

eters of antiMAG NP patients treated with BTKi at the Padova University Hospital since January 2019.

To report the efficacy and safety of BTK inhibitors (BTKi) in patients with antiMAG NP.

Eleven antiMAG NP patients (8 men, median age 74yrs, range 48-82) were treated with BTKi, 6 ibrutinib and 5 zanubrutinib. All patients had a Waldenström macroglobulinemia, 91% harboring MYD88 L265P but not CXCR4 S338X mutations, and demyelinating neuropathy.

The median duration of antiMAG NP was 6.9 yrs (range 0.7-18 yrs) and all patients had received at least 1 previous cycle of Rituximab (range of previous therapy 1-4).

63.6% of patients had a clinical improvement as best response, defined as decrease of at least 1 point in 2 neurological scale (INCAT, ISS, MRC), while 4 patients stabilized (Fig. 1A).

After a median follow-up of 32 months (45.5 ibrutinib and 15 zanubrutinib) the estimated median duration of response was 50.5 months (Fig. 1B). All patients showed a decrease of paraprotein and IgM, after 12 months ($p < 0.001$).

One patient discontinued BTKi due to COVID19-related death. Two other patients died for worsening of concomitant Parkinson's disease and one for severe depression.

BTKi seem active and safe in antiMAG NP, being able to control the disease in most of patients.

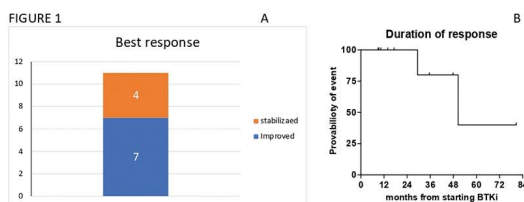


Figure 1. A. Distribution of best clinical response to BTK inhibitors assessed by neurological scales (INCAT, ISS, MRC). B. Kaplan-Meier curve showing the duration of clinical response to BTK inhibitors in patients with anti-MAG antibody neuropathy

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143502

EVOLVING ELECTROPHYSIOLOGICAL PATTERNS IN CIDP: HOW ELECTROPHYSIOLOGICAL PATTERNS CAN INFORM TREATMENT RESPONSE AND RECOVERY

Fiumarella R.^{*1}, Cassano E.², Castiglia M.¹, Aiello A.¹, Dell'Aversana D.¹, Canale F.³, Nolano M.¹, Manganelli F.¹, Tozza S.¹
¹ Department of Neuroscience, Reproductive and Odonstomatological Science, University of Naples Federico II, Naples, Italy, ² Neurology Unit, Ospedale del Mare, Naples, Italy, ³ Neurology Unit, University Hospital Federico II, Naples, Italy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is the most common acquired immune-mediated chronic neuropathy, with heterogeneous clinical and electrophysiological features.

To characterize electrophysiological patterns in CIDP and their rela-

tionship with clinical response. We retrospectively analysed 30 CIDP patients (21 male; mean age at onset 44.5 ± 18.9 years; disease duration 1.58 years) at baseline and last available evaluation. Based on the distribution of electrophysiological abnormalities, patients were classified as distal, intermediate, proximal, or mixed. Clinical variables, including age at onset, sex, disease duration, baseline and follow-up INCAT scores, and treatment response, were evaluated in relation to electrophysiological patterns.

At baseline, patterns were distal in 13.3%, intermediate in 30%, proximal in 33.3%, and mixed in 23.3%. Patterns did not differ by age, sex, disease duration, or disability. Following treatment, 53.3% improved, 33.3% remained stable, and 13.3% worsened. Response to treatment differed across demyelinating categories, driven by distal (100%) and mixed (14.3%) patterns ($p = 0.046$). At last evaluation, patterns changed: distal 3.3%, intermediate 23.3%, proximal 13.3%, mixed 26.6%, and normal in 33.3%. Clinical improvement was associated with normalization (81.1%) or proximal demyelination (100%) ($p = 0.021$).

Electrophysiological patterns in CIDP are heterogeneous and may evolve over time. Baseline distal and mixed patterns are linked to differential treatment response, while clinical improvement correlates with normalization or proximal demyelination, underscoring the prognostic value of serial electrophysiological assessment.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 143431

NEURALGIC AMYOTROPHY ULTRASOUND CHARACTERISTICS: A SINGLE CENTER STUDY

Carta S.^{*2}, Schiavi G.M.¹, Pasquali A.¹, Cazzoli S.¹, Usai G.¹, Tamburin S.², Zanette G.¹

¹ Neurology Unit, Pederzoli Hospital, Peschiera del Garda, Italy, ² Neurology Unit, Department of Neurosciences, Biomedicine, Movement Sciences, University of Verona, Verona, Italy

Neuralgic amyotrophy (NA) presents with severe upper-extremity pain followed by multifocal paresis. Despite previous assumptions of a favorable prognosis, many patients develop persistent deficits. Nerve enlargement and hourglass constrictions (HC) can be detected on ultrasound or MRI, and HC have been linked to poorer outcomes. Pederzoli hospital provides the only nerve ultrasound service in Verona province.

This study evaluated the frequency and ultrasound characteristics of NA at our centre

Patients diagnosed with NA within the preceding 12 months and evaluated with nerve ultrasound between April 2024-January 2026 were retrospectively enrolled. Clinical/ultrasound data were collected in a dedicated database. Among 1244 patients evaluated, 31 met inclusion criteria. Median age at onset was 46.1 years [IQR 34.9–57.5]; 25 (80.6%) were male. Median time from symptom onset to ultrasound was 4.64 months [IQR 1.62–6.88]. NA was bilateral in one patient, 21 (67.7%) had multifocal involvement. The most frequently affected sites were cervical nerve roots (C5 n = 6, C6 n = 5), median (n = 9, 29%), suprascapular (n = 8), and radial nerve (n = 6).

Nerve enlargement was observed in 27 patients (84.4%). HC were detected in 11 patients (32.2%), involving the suprascapular, median, radial, musculocutaneous nerves, and C5–C6 roots. Detailed clinical data were available for 23 patients. Severe motor deficit (MRC 0–1) was present in 5 (23.8%), moderate (MRC 2–3) in 10 (43.5%), and mild (MRC 4–5) in 6 (26.1%). HC were not significantly associated with worse motor function at evaluation ($p = 0.104$).

NA is relatively frequent, and nerve ultrasound is a valuable diagnostic tool, with abnormalities present in most patients.



THURSDAY, MAY 14TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N. 8

Modular Parallel Room 3

Chairs: Roberta Massa, Elena Saccani

MUSCULAR DYSTROPHIES

ABSTRACT COD. 143319

OCULOPHARYNGEAL MUSCULAR DYSTROPHY: A MULTICENTER RETROSPECTIVE COHORT ANALYSIS FROM THE ITALIAN NETWORK

Alberti C.¹, Gagliardi D.², Primiano G.³, Arena I.G.⁴, Zoppi D.⁵, Ricci G.⁶, Cheli M.⁷, Croce M.G.⁸, Gadaleta G.⁹, Valentino M.L.¹⁰, Faedo E.¹¹, Verriello L.¹², Colacicco G.¹³, Laurini C.¹⁴, Risi B.¹⁵, Loperigolo D.¹⁶, Sancricca C.¹⁷, Servidei S.³, Briganti M.¹⁷, Ardito M.³, Siciliano G.⁶, Giacomuzzi Grigoli E.⁷, Falzone Y.M.¹⁴, Velardo D.¹⁸, Magri F.¹⁸, Moliterno N.¹⁸, Parisi M.², Sciacco M.¹⁸, Moggio M.¹⁸, Filosto M.¹⁵, Previtali S.C.¹⁴, Sansone V.¹³, Grandis M.¹¹, Liguori R.¹⁰, Mongini T.E.⁹, Ravaglia S.¹⁹, Maggi L.⁷, Mancuso M.⁶, Ruggiero L.⁵, Musumeci O.⁴, Toscano A.⁴, Mirabella M.³, Comi

G.P.¹, Ronchi D.¹, Corti S.P.¹

¹ Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, ² IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy, ³ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ⁴ Unit of Neurology and Neuromuscular Disorders, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ⁵ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy, ⁶ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ⁷ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy, ⁸ Department of Brain and Behavioural Sciences, University Of Pavia, Pavia, Italy, ⁹ Neuromuscular Unit, Department of Neurosciences 'Rita Levi Montalcini', University of Turin, Turin, Italy, ¹⁰ IRCCS Istituto delle Scienze Neurologiche di Bologna, University of Bologna, Bologna, Italy, ¹¹ Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINO GMI), University of Genoa, Genoa, Italy, ¹² Neurology Unit, Head-Neck and Neurosciences Department, Santa Maria della Misericordia University Hospital, Udine, Italy, ¹³ The NeMO Clinical Center in Milan, Milan, Italy, ¹⁴ Neuromuscular Repair Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy, ¹⁵ NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ¹⁶ Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, ¹⁷ Fondazione UILDM Lazio Onlus, Rome, Italy, ¹⁸ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular and Rare Disease Unit, Milan, Italy, ¹⁹ Neuromuscular Unit, IRCCS C. Mondino Foundation, Pavia, Italy

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant, late-onset myopathy with progressive ptosis, dysphagia, and proximal limb weakness. Small expansions of the (GCN)_n trinucleotide in PABPN1 modulate age at onset and disease severity.

We retrospectively analyzed 205 genetically confirmed OPMD patients from 15 Italian neuromuscular centers. Clinical and genetic features were assessed; available muscle biopsies were reviewed. The relationship between GCN repeat size and age at onset was evaluated using non-parametric tests and linear regression.

The cohort included 107 males and 98 females (mean age at onset 55 ± 10.6 years; evaluation 64.1 ± 12.6 years; diagnostic delay 8.5 ± 7.5 years). Ptosis (31.8%) and dysphagia (29.7%) were the most frequent initial manifestations; 81.8% remained ambulatory. Family history was positive in 82.9%. Most patients were heterozygous for GCN expansions (10–15 repeats), with 10–13 repeats being most common (47.6%). Homozygous expansions occurred in 14 (6.8%), and one patient carried the PABPN1 c.35G > C variant. Larger expansions were associated with earlier age at onset (10–13 vs. 10–12, $p = 0.027$; 10–14 vs. 10–12, $p = 0.0008$); linear regression confirmed an inverse correlation (slope -2.2 years/repeat, $R^2 = 0.82$, $p = 0.005$). Muscle biopsies ($n = 23$) revealed rimmed vacuoles in 50%, and PABPN1 immunohistochemistry was positive in 65.2%.

To our knowledge, this represents the second largest OPMD cohort in Europe. This large Italian cohort confirms the classical late-onset, slowly progressive phenotype dominated by ptosis and dysphagia, and provides comprehensive genotype-phenotype correlations. These findings improve understanding of OPMD, support prognostic counseling, and may guide future trials.

MYOTONIC DYSTROPHIES**Abstract Cod. 143409****THE NOVEL (TCTG)N MOTIF IN CNBP EXPANDED ALLELES: COMPOSITION, DYNAMICS AND GENOTYPE-PHENOTYPE CORRELATION IN DM2**

Centofanti F.^{*1}, Visconti V.V.¹, D'Apice M.R.², Carlomagno M.³, Mestri S.³, Ciabini D.¹, Bengala M.², Marchionni E.², Frezza E.⁴, Massa R.⁴, Petrucci A.⁵, Lupidi F.⁶, Pegoraro E.⁷, Siciliano G.⁸, Garibaldi M.⁹, Origone P.¹⁰, Delledonne M.³, Rossato M.³, Botta A.¹, Novelli G.¹

¹ Department of Biomedicine and Prevention, Medical Genetics Section, University of Rome Tor Vergata, Rome, Italy, ² Laboratory of Medical Genetics, Tor Vergata Hospital, Rome, Italy, ³ Department of Biotechnology, University of Verona, Verona, Italy, ⁴ Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy, ⁵ Center for Neuromuscular and Neurological Rare Diseases, S. Camillo Forlanini Hospital, Rome, Italy, ⁶ Neurological Clinic, Azienda Ospedaliera Universitaria delle Marche, Ancona, Italy, ⁷ Azienda Ospedale Università Padova, Padova, Italy, ⁸ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ⁹ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ¹⁰ IRCCS Azienda Ospedaliera Metropolitana, Genova, Genova, Italy

Myotonic dystrophy type 2 (DM2) is an autosomal dominant disorder caused by (CCTG)n repeat expansions in intron 1 of the CNBP gene. Recent evidence from long-read sequencing suggests these expansions may be more complex than previously recognized.

To comprehensively characterize the composition, intergenerational dynamics, and clinical impact of novel (TCTG)n motifs within the CNBP expanded alleles in a large DM2 cohort.

We analyzed 100 genetically confirmed DM2 individuals (45 sporadic, 55 familial). The presence of (TCTG)n blocks was detected using an optimized quadruplet-repeat primed PCR (QP-PCR) assay coupled with Sanger sequencing. In a subset of nine patients, Cas9-mediated sequencing provided nucleotide-level resolution of the expanded alleles. We identified (TCTG)n blocks at the 3' end of the expansion in 88% of patients. This refined assay corrected nine initial false-negative diagnoses from standard testing. LRS analysis confirmed the composition and revealed the dynamics of the (TCTG)n tract in familial transmission, showing a tendency for contraction and, in one case, complete loss. Genotype-phenotype correlation analysis indicated that the presence of the (TCTG)n motif acts as a disease modifier, significantly influencing the age of onset.

The detailed characterization of the CNBP expansion reveals the novel (TCTG)n component that is integral to the DM2 genotype. Understanding its composition and dynamics enhances diagnostic accuracy and provides a new framework for genetic counselling, prognostic stratification and future personalized therapies.

This research was funded by the European Union—Next Generation EU—NRRP M6C2—Investment 2.1 Enhancement and strengthening of biomedical research in the NHS.

MYOTONIC DYSTROPHIES**Abstract Cod. 143030****PLASMA PTAU-181 AS A PROGNOSTIC BIOMARKER OF MOTOR DECLINE IN MYOTONIC DYSTROPHY TYPE 1**

Frezza E.^{*1}, Goglia M.², Petitta I.², Greco G.³, Gruosso F.², Vietri G.⁴, Boffa L.⁵, Centonze D.⁶, Nuccetelli M.⁷, Massa R.⁸

¹ Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; IRCCS Neuromed, Pozzilli (IS), Italy, Rome, Italy, ² Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, Rome, Italy, ³ Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; Unit of Neurology, AOU Policlinico Tor Vergata, Rome, Italy, Rome, Italy, ⁴ Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy; IRCCS Neuromed, Pozzilli (IS), Italy, Rome, Italy, ⁵ Unit of Neurology, AOU Policlinico Tor Vergata, Rome, Italy, Rome, Italy, ⁶ Department of Systems Medicine, Tor Vergata University of Rome; Unit of Neurology, AOU Policlinico Tor Vergata, Rome, Italy; IRCCS Neuromed, Pozzilli (IS), Italy, Rome, Italy, ⁷ Unit of Laboratory Medicine, AOU Policlinico Tor Vergata, Rome, Italy, Rome, Italy, ⁸ Unit of Neuromuscular Diseases, Department of Systems Medicine, Tor Vergata University of Rome, Rome; Unit of Neurology, AOU Policlinico Tor Vergata, Rome, Italy; IRCCS Neuromed, Pozzilli (IS), Italy, Rome, Italy

Myotonic dystrophy type 1 (DM1) is a slowly progressive multisystem disorder affecting skeletal muscle, heart, and central nervous system (CNS). The lack of non-invasive prognostic biomarkers limits prediction of disease progression in DM1. Given CNS involvement in DM1, biomarkers of neurodegeneration may provide information on disease evolution. This study aimed to evaluate biomarkers of neurodegeneration in relation to inflammation, metabolic status, and motor function and to explore their association with longitudinal motor disease progression.

In this longitudinal study, 92 genetically confirmed DM1 patients were enrolled. Motor performance and fatigue were assessed using the 6-Minute Walk Test (6MWT) and the Fatigue severity scale (FSS). Plasma levels of neurofilament light chain (NfL), pTau-181, glial fibrillary acidic protein (GFAP), and interleukin-6 (IL-6) were measured. Creatine kinase (CK) and the HOMA index were collected as markers of muscle damage and metabolic status. Associations were evaluated using cross-sectional analyses and linear mixed-effects models. Plasma pTau-181 showed a significant positive correlation with CK ($r = 0.45$ $p < 0.001$). NfL was inversely associated with 6MWT and positively correlated with IL-6 and GFAP. Patients with insulin resistance exhibited higher IL-6, BMI, and FSS score, together with lower 6MWT performance. Longitudinal analyses showed that pTau-181 was not associated with baseline motor severity but significantly predicted motor decline over time, with higher levels indicating faster deterioration ($\beta = -3.67$ $p = 0.027$).

Plasma pTau-181 parallels muscle damage and emerges as a promising non-invasive prognostic biomarker of motor decline in DM1. Insulin resistance characterizes patients with poorer motor function and higher IL-6.

MYOTONIC DYSTROPHIES

Abstract Cod. 143411

CIRCULATING MUSCLE-SPECIFIC MIRNAS UNCOVER DIFFERENTIAL MOLECULAR SIGNATURES IN MYOTONIC DYSTROPHY TYPE 1 AND 2 PATIENTS

Ciabini D.^{*1}, Visconti V.V.¹, Centofanti F.¹, Frezza E.², Goglia M.², Greco G.², Massa R.², Novelli G.¹, Botta A.¹

¹ Department of Biomedicine and Prevention, Medical Genetics Section, University of Rome "Tor Vergata", Via Montpellier 1, 00133 Rome, Italy., Rome, Italy, ² Department of Systems Medicine (Neurology), University of Rome Tor Vergata, Rome, Italy., Rome, Italy

Myotonic dystrophy type 1 (DM1, MIM# 160900) and type 2 (DM2, MIM#602668) are autosomal dominant multisystemic disorders, caused by non coding expanded (CTG)_n and (CCTG)_n, respectively. Although both diseases share overlapping clinical features, they differ in age of onset, disease progression and severity. Since reliable circulating biomarkers are still lacking, this work focuses on the study of muscle-specific microRNAs (myomiRNAs), which have emerged as promising candidates.

Plasma samples were obtained from healthy controls (n = 25), DM1 (n = 70) and DM2 (n = 30) patients. The expression of miRNA-1-3p, miRNA-133b, and miRNA-206 was quantified by real-time PCR. Raw results have been analyzed using the ΔC_t method. Group comparisons were performed on ΔC_t values using one-way ANOVA. Relative expression levels were calculated using the $2^{-\Delta\Delta C_t}$ method.

Circulating levels of all the myomiRNAs analyzed were significantly increased in DMs patients compared to controls. Notably, miRNA-133b and miRNA-206 showed pronounced upregulation (fold changes of 2.73 and 3.57, respectively), while miR-1-3p exhibited a more moderate increase (fold change 1.44). Stratified analysis revealed distinct expression profiles between DM1 and DM2, with higher dysregulation observed in DM1 (miRNA-133b) or DM2 (miRNA-1-3p and miRNA-206) samples.

This study demonstrates that circulating myomiRNAs are dysregulated in DMs patients' plasma, displaying disease-specific expression patterns. These findings strongly support their use as non-invasive biomarkers for disease stratification, prognosis and therapeutic monitoring in clinical trials.

OTHERS

Abstract Cod. 143046

INTEGRATED ORTHOPEDIC AND NEUROLOGICAL 14-YEAR EXPERIENCE IN THE DIAGNOSTIC APPROACH TO THE 'TOE WALKER' SPECTRUM IN A PEDIATRIC POPULATION

Trentin E.^{*1}, Giannotta M.¹, Scarpini G.¹, Palombo F.², Trisolino G.³, Di Gennaro G.L.³, Pini A.¹

¹ UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS ISNB Istituto delle Scienze Neurologiche di

Bologna, Ospedale Bellaria, Bologna, Italy, ² Programma di Neurogenetica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ UOC Ortopedia Pediatrica, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy

Toe walking is a common isolated feature in pediatric age, and Idiopathic Toe Walking (ITW) is a particularly frequent exclusion diagnosis, with a reported prevalence of 5–12% at ~5 years of age (Bauer, 2022; Pomarino, 2025). However, in 16–17% of cases, toe walking may conceal an underlying neuromuscular or neurological disorder (Bauer, 2022; Pomarino, 2025; Pomarino, 2023; Veerkamp, 2024). We retrospectively collected data on patients referred for toe walking and evaluated at an integrated outpatient clinic involving the Regional Pediatric Neuromuscular Centre of IRCCS-ISNB and the Pediatric Orthopaedic Unit of IRCCS-IOR in Bologna, focusing on pre-surgical diagnostic evaluation in patients with ankle contractures.

Over the 14-year period, 297 patients (M = 205, F = 92; mean age at first assessment: 7.6) were evaluated. Patients underwent a detailed clinical history, neurological and neuromuscular examination, with emphasis on toe walking onset and progression, and serum CK testing. They were classified as ITW with isolated ankle contractures (70%) or TW-plus in cases of contractures involving multiple districts (1%). Further investigations (ENG; brain, muscle or spinal MRI; muscle biopsy; NGS) were performed in TW-plus cases and in TW with onset ≥ 3 years. Nuclear envelope muscle dystrophy, calpainopathies, peripheral neuropathies, genetic or acquired spastic paraparesis, subtle congenital hemiplegia, and spinal cord lesions were diagnosed. Ultra-rare mutations were also discovered.

We emphasize the value of an integrated neurology-orthopedics approach, and propose a new classification of TW with ankle contractures, which represents a key symptom that can help with early diagnosis of genetic neuromuscular diseases.

MYOTONIC DYSTROPHIES

Abstract Cod. 142950

CLINICAL SPECTRUM OF MYOTONIC DYSTROPHY TYPE 2: RESULTS FROM A CROSS-SECTIONAL MONOCENTRIC STUDY

Faedo E.^{*1}, Massucco S.¹, Barone C.¹, Bruzzone V.², Gemelli C.², Mandich P.¹, Gotta F.², Schenone A.², Grandis M.¹

¹ Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINO GMI), University of Genoa, Genoa, Italy, ² IRCCS Ospedale Policlinico San Martino, Azienda Ospedaliera Metropolitana (AOM), Genoa, Italy

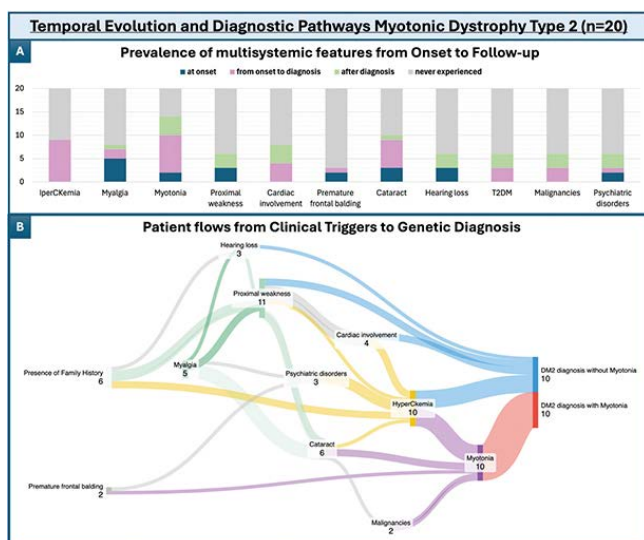
Myotonic dystrophy type 2 (DM2) is a multisystem disorder frequently underdiagnosed due to heterogeneous and non-specific early manifestations, leading to prolonged diagnostic delays.

We retrospectively analyzed 20 genetically confirmed DM2 patients (65% female, n = 13) followed at a single tertiary center, evaluating the temporal evolution of neuromuscular and multisystem features and the interval between symptom onset and genetic diagnosis.

The mean diagnostic delay was 9.5 ± 8.9 years. Family history facilitated the diagnostic process in 6 patients (30%), and three families originated from Eastern Europe. At onset, myalgia was the most frequent symptom (25%, n = 5), followed by proximal weakness,

cataracts, and hearing loss (15% each, $n = 2$) (Figure 1A). HyperCKemia (> 300 U/L) was detected in 10 patients (50%) and ranged from asymptomatic elevations ($n = 1$) to recurrent rhabdomyolysis ($n = 1$). Patients identified through hyperCKemia showed a trend toward shorter diagnostic delay ($p = 0.081$). Although myotonia ultimately affected 14 patients (70%), ten (50%) were diagnosed in its absence, with diagnostic suspicion driven by family history, hyperCKemia, and cataracts (50% each, $n = 5$), among other features (Figure 1B). Psychiatric disorders, including bipolar disorder and depression, occurred in 6 patients (30%), and gynecological complications, were observed in 6 women (46%). Malignancies occurred in 6 patients (30%) and were significantly more frequent in those presenting with myotonia at diagnosis ($p = 0.011$).

DM2 diagnosis is often delayed until highly specific features, like myotonia, appear. Early genetic testing in unexplained hyperCKemia may reduce diagnostic delay and allow timely identification of multi-system complications, suggesting the need to carefully monitor on-cological manifestations in myotonic patients.



THURSDAY, MAY 14TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N. 9

Modular Parallel Room 3

Chairs: Emily Bellone, Marco Savarese

EXPERIMENTAL THERAPIES

Abstract Cod. 143473

A UNIVERSAL DONOR CELL FOR THE NEXT

GENERATION CELL AND EX VIVO GENE THERAPIES

Cossu G.*, Tonlorenzi R., Perani L., Proietti D.
San Raffaele Hospital, Milan, Italy

Cell therapy and ex vivo gene therapy are facing important economic issues that have caused withdrawal from the market of approved and curative protocols. Indeed, these are extreme forms of "precision medicine" where an extremely expensive medicinal product can be used for a patient only. To overcome this problem many groups are developing until now only ES and iPS cells, devoid of HLA and expressing molecules blunting the immune response. However after long in vitro culture, ES and iPS cells develop chromosome aberrations that have limited their clinical translation.

To develop a universal, immune privileged adult progenitor cells for monogenic disorders of muscle

Edited cells continue to proliferate and differentiate as primary non modified cells, they show a normal karyotype, maintain growth factor dependence for proliferation and are not tumorigenic in immune deficient mice. In vitro test showed that they do not activate CD4, CD8 or NK cells, while transplantation in injured muscles of immune deficient mice, confirmed their persistence after 40 days from the injection while control, non-edited cells are no longer detectable. These findings show that it is possible to render adult mesoderm cells invisible to the immune system and these cells can be amplified to create GMP banks of mesoderm progenitors tailored for a specific genetic disease. Thus one single GMP preparation of immune invisible cells, may be used for many patients, thus cutting in proportion the cost/patient.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 142697

PATIENT-DERIVED SPINAL CORD ORGANOID REVEAL CRITICAL TREATMENT WINDOWS IN SMA

Corti S.*¹, D'Angelo A.², Beatrice F.², Cordiglieri C.³, Miotto M.⁴, Lodato S.⁴, Gagliardi D.⁵, Comi G.¹, Rizzo F.⁵, Ottoboni L.¹

¹ University of Milan, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ² University of Milan, Milan, Italy, ³ INGM, Milano, Italy, ⁴ Humanitas University, Milan, Italy, ⁵ Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy

SMN-restoring therapies have transformed SMA treatment, yet optimal intervention timing remains a critical clinical challenge. Understanding the temporal dynamics of neurodegeneration and therapeutic response is essential for maximizing outcomes. Human spinal cord organoids offer a unique platform to investigate these questions in a physiologically relevant context.

To identify optimal therapeutic windows for SMN2 modulation and characterize novel pathogenic mechanisms in SMA using patient-derived spinal cord organoids.

Three-dimensional spinal cord organoids were generated from SMA patient-derived iPSCs using an innovative scaffold-free protocol. Multielectrode array recordings revealed profound neurophysiologi-

cal deficits in SMA organoids, including reduced spontaneous firing rate and disrupted network synchronization. RNA sequencing uncovered extensive downregulation of ciliary genes, suggesting a novel pathogenic mechanism. Treatment with the SMN2 splicing modifier RO7021707 (Risdiplam-like) demonstrated striking temporal specificity: intervention during intermediate differentiation achieved optimal SMN restoration and normalized network activity, while earlier treatment showed partial recovery and later intervention provided minimal benefit.

Our findings identify ciliary dysfunction as a novel contributor to SMA pathogenesis and define precise temporal windows for optimal therapeutic intervention. These results carry direct implications for treatment timing and suggest ciliary pathways as potential therapeutic targets.

NEUROBIOLOGY

Abstract Cod. 143263

MORPHOLOGICAL AND MOLECULAR ALTERATIONS IN THE SOMATOSENSORY CORTEX VASCULATURE OF RATS WITH PACLITAXEL-INDUCED PAINFUL PERIPHERAL NEUROPATHY

Zippo A.G.¹, Donà E.¹, D'Aprile C.², Sacchini A.¹, Canta A.², Chiorazzi A.², Pozzi E.², Rodriguez--Menendez V.², Ballarini E.², Piazza R.³, D'Aliberti D.³, Tromba G.⁴, Alberti P.², Meregalli C.², Cerchi L.², Cavaletti G.², Carozzi V.A.*²

¹ Institute of Neuroscience, Consiglio Nazionale delle Ricerche, Veduggio al Lambro (Italy), Italy, ² Experimental Neurology Unit, University of Milan Bicocca, Monza, Italy, ³ University of Milan Bicocca, Monza, Italy, ⁴ Elettra-Sincrotrone Trieste S.C.p.A, Basovizza, Trieste (Italy), Italy

Painful paclitaxel-induced peripheral neurotoxicity (PPIP) is a common dose-limiting side effect of the anticancer drug paclitaxel, characterized by paresthesia, numbness, and neuropathic pain. While research historically focused on peripheral neurons, recent evidence suggests that microvascular angiogenesis within the somatosensory pathway plays a critical role in pain development.

This study investigates time-dependent vascular and molecular alterations in the S1 cortex during the onset and chronicization of PIPN. Rats received 10 mg/kg of paclitaxel weekly for four weeks. Longitudinal evaluation of neurophysiological/morphological abnormalities and neuropathic pain-24 hours post-infusion, after two weeks, at the end of treatment, and after a four-week follow-up-revealed that paclitaxel induces irreversible, dose-dependent peripheral nerve damage and neuropathic pain starting at week two.

Concomitantly, we performed a quantitative vascular network organisation analysis at sub-micrometric resolution through X-ray Phase-Contrast Tomography (XPCT). These results show a persistent increase in vascular density in S1 cortex, suggestive of sprouting angiogenesis, though leading to smaller and less complex vessels.

To investigate the genetic signature signatures and angiogenic molecules associated with PIPN, we employed single-nucleus RNA sequencing (snRNAseq). Preliminary transcriptomic data highlight significant molecular alterations across cellular populations. Notably,

the transcription factor Rbfox1, previously associated with blood-brain-barrier permeability, appears to be specifically increased in endothelial cells. Beyond morphological rearrangements of the vascular network, these findings raise the possibility of functional alterations. Our data identified key neurovascular alterations in the somatosensory cortex accompanying PPIP development, potentially revealing new targets for neuroprotective interventions.

Funded by Ministero dell'Università e della Ricerca, PRIN 2022 ID 2022NBS28K, PI V.A. Carozzi.

NEUROBIOLOGY

Abstract Cod. 143412

ROLE OF UNCONVENTIONAL MYOSIN1B IN PERIPHERAL NERVOUS SYSTEM

Capodivento G.*¹, Visigalli D.², Camera M.¹, Di Patrizi I.¹, Schenone A.², Nobbio L.¹

¹ IRCCS Azienda Ospedaliera Metropolitana, Genova, Italy, ² Università degli studi di Genova, Genova, Italy

Cytoskeletal alterations are critical for the morphogenesis of glial cells, and actin polymerization and depolymerization are involved in cell differentiation and myelin wrapping. The main partners of cortical actin are molecular motors of the myosin superfamily. In particular, the single-headed myosin 1 proteins (Myo1), bridges cortical actin to the plasma membrane via the PH domain. This unconventional myosin superfamily was largely described in CNS as regulator of myelin structure and growth cone. However, the role of Myo1 has never been investigated during myelination in the PNS.

Grounding on data from our group on gene expression profiling performed on WT and CMT1A rat sciatic nerves, we deeply explored cytoskeleton and muscle pathways in adult PNS and during development.

We identified, for the first time, a class 1 myosin (Myo1B) in specific domains of PNS myelinated tissue, namely Schmidt-Lanterman incisures (SLIs). The co-localization of Myo1B with typical proteins of SLIs confirmed the specific location. Actually, we found an aberrant expression and positioning of Myo1B in adult CMT1A rat myelinated fibers. In particular, Myo1B is expressed in non-canonical shapes highly repeated along the entire fiber instead the regularly and periodically spaced V-shaped configuration displayed in physiological condition. Aberrant expression and mislocalization of Myo1B in myelinated CMT1A fibers were evident early in development (P10). We identified a critical structural role of the unconventional Myo1B in PNS development and its derangement in a well-known dysmyelinating neuropathy namely CMT1A. Acto-myosin cytoskeleton could be a novel therapeutic target to unlock the immature stage of CMT1A PNS.

MUSCULAR DYSTROPHIES

Abstract Cod. 143081

NEW INSIGHTS INTO THE MOLECULAR ROLE OF TNPO3 IN A ZEBRAFISH MODEL OF LGMD2

Rodia M.T.^{*1}, Fazzina M.², Costa R.¹, Brighi G.³, Altieri M.T.⁴, Breveglieri G.⁴, Sabbioni G.⁴, Gatto E.⁴, Bertolucci C.⁴, Casadei R.⁵, Ratti S.¹, Ascoli S.¹, Cenacchi G.¹, Borgatti M.⁴, Frabetti F.³

¹ Department of Biomedical and Neuromotor Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy, Bologna, Italy, ² Department of Pharmacy and Biotechnology, Alma Mater Studiorum University of Bologna, Bologna, Italy, Bologna, Italy, ³ Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy, Bologna, Italy, ⁴ Department of Life Sciences and Biotechnology, University of Ferrara, Ferrara, Italy, Ferrara, Italy, ⁵ Department for Life Quality Studies, Alma Mater Studiorum University of Bologna, Bologna, Italy, Bologna, Italy

Zebrafish (*Danio rerio*) is a powerful in vivo model for human developmental studies due to the high conservation of key biological processes between zebrafish and humans. In this work, we developed an in vivo model to explore the role of Transportin 3 (TNPO3) in skeletal muscle development. TNPO3 is a nuclear import receptor for serine/arginine-rich proteins, which play a crucial role in mRNA splicing and metabolism. Mutations in the TNPO3 gene have been associated with a dominant form of limb-girdle muscular dystrophy, known as LGMD2; however, the molecular mechanisms driving disease progression are still poorly understood.

To address this, we established a zebrafish model by microinjecting embryos with mRNA encoding either the wild-type (WT) or mutant (MUT) human TNPO3 (hTNPO3).

Using molecular, structural, and functional behavioral analyses, we provide the first evidence supporting a role for TNPO3 in the regulation of myogenesis. These findings were further extended through knockdown of the endogenous *tnpo3* gene using Morpholino antisense oligonucleotides (MOs). Gene expression analyses of myogenesis-associated markers in morphant embryos confirmed a strong association between TNPO3 activity and muscle development. Additionally, the combined microinjection of MOs with MUT hTNPO3 mRNA enables the generation of an even more accurate disease model to uncover the relationship between TNPO3 mutations and LGMD2 pathogenesis.

Overall, our findings reinforce the critical role of TNPO3 in myogenesis and provide an in vivo system that recapitulates key pathological features of LGMD2 representing also a promising platform for drug screening and repurposing strategies to identify effective therapies for LGMD2.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143410

THE MYOSTATIN-SMAD3 PATHWAY AS BIOMARKER FOR MONITORING DISEASE COURSE UNDER DISEASE-MODIFYING THERAPIES IN SPINAL MUSCULAR ATROPHY

Riolo G.^{*1}, Giacomuzzi Grigoli E.¹, Cheli M.¹, Parravicini S.², Canciello A.¹, Andreetta F.¹, Dosi C.², Bonanno S.¹, Marcuzzo S.³, Masson R.², Maggi L.¹

¹ Neurology 4 - Neuroimmunology and Neuromuscular Diseases Unit – Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ² Developmental Neurology Unit– Fondazione IRCCS Istituto Neurologico

Carlo Besta, Milano, Italy, ³ Brain-targeted Nanotechnologies (BrainNs) Lab, Joint Research Platform – Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy

Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disorder characterized by motor neuron loss and progressive muscle atrophy. Identifying biomarkers is crucial to monitor disease progression and response to disease-modifying therapies (DMTs).

Given Myostatin's (MSTN) role in muscle regulation and its modulation by SMA therapies, we investigated serum MSTN and its downstream effector Smad3, assessed as novel potential SMA biomarkers. The study included pediatric and adult SMA patients receiving DMTs as monotherapy (Nusinersen = 15; Risdiplam = 15), and participants in anti-MSTN trials (n = 7), whose data were analysed only at baseline. Serum MSTN and Smad3 levels were measured by ELISA at baseline, 6 and 14 months post-treatment in pediatric and adult SMA patients respectively, considering slower DMTs effects in adulthood. Median MSTN levels at baseline were significantly higher in: males (893.1 pg/mL; 204.4–2405.9) vs female (569.4 pg/mL; 256.5–985.1); SMA type III (830.8 pg/mL; 292.5–1648.0) vs type II (475.4 pg/mL; 204.4–2405.9), and walkers (954.4 pg/mL; 361.9–2405.9) vs non-sitters (344.9 pg/mL; 204.4–675.1). Smad3 showed no differences. MSTN and Smad3 remained stable during treatment and were not influenced by the therapy type. In adults, MSTN positively correlated with HFMSE motor scale at baseline (r = 0.58, p < 0.05) and post-treatment (r = 0.67, p < 0.01). In pediatric patients, MSTN fold change and post-treatment Smad3 were negatively correlated with HFMSE improvement (r = -0.75, p < 0.01) and RULM scores (r = -0.65, p < 0.05), respectively.

These findings support MSTN and Smad3 as biomarkers of SMA severity and functional status, with MSTN potentially monitoring treatment-related motor changes in pediatric patients, likely reflecting greater muscle plasticity.

FRIDAY, MAY 15TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N.10

Modular Parallel Room 1-2

Chairs: Melania Giannotta, Marika Pane

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143271

MULTI-OMIC BIOMARKERS ENABLE PERSONALIZED SMA MANAGEMENT IN A MULTICENTER ITALIAN STUDY

Panicucci C.^{*1}, Ottoboni L.², Errico F.³, Usiello A.³, Rizzo F.², Beatrice F.², Marcotti F.², Petretto A.¹, Bartolucci M.¹, Fiorillo C.¹, Brolatti N.¹, Gagliardi D.², Onorato G.⁴, Torre A.M.⁵, Romani S.⁵,

Sansone V.⁶, Di Schiavi E.⁴, Aguenouz M.⁵, Corti S.², Bruno C.¹

¹ IRCCS Istituto Giannina Gaslini, Genova, Italy, ² Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy, ³ CEINGE Biotechnologie Avanzate, Napoli, Italy, ⁴ CNR-IBBR, Napoli, Italy, ⁵ Policlinico G. Martino, Messina, Italy, ⁶ Nemo Center, Milano, Italy

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder caused by mutations in the SMN1 gene, leading to degeneration of motor neurons and progressive muscle atrophy. Although recent therapeutic advances and the availability of three approved treatments, clinical management remains challenging due to the heterogeneous disease course and the limited ability to predict treatment outcomes. Reliable biomarkers are therefore urgently needed to support prognosis and personalized therapeutic decisions.

To identify and validate multi-omic biomarkers for personalized SMA management across a multicenter Italian cohort.

Biological samples from SMA patients (Types 1–3), undergoing different treatments, and controls were analyzed across three Italian centers using proteomics, metabolomics, lipidomics, and DNA methylation profiling. Clinical assessments and serum collection were performed at baseline and after 12 months. Proteomics revealed dysregulation of axon guidance molecules, including reduced NRXN2 expression and altered SEMA6A/7A levels. HPLC metabolomics showed that the L-glutamine/L-glutamate ratio distinguished SMA subtypes and normalized after nusinersen in Type 1 patients. Elevated D-serine/total serine ratios in more severe phenotypes correlated with CHOP-INTEND scores. Machine learning identified three molecular clusters predictive of treatment response. Patient-derived spinal cord organoids and *C. elegans* SMA models recapitulated key molecular signatures, supporting biomarker validity.

Serum proteomic and metabolomic alterations, particularly within amino acid pathways, emerged as potential biomarkers of SMA severity and response to nusinersen. Integration with machine learning and experimental models supports their biological relevance, although further validation is required for clinical translation. Expanded multi-omic profiling may uncover convergent molecular signatures associated with clinical heterogeneity and treatment response in SMA.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143360

SUSTAINED MOTOR FUNCTION STABILIZATION IN TREATED ADULT SPINAL MUSCULAR ATROPHY: REAL-WORLD EVIDENCE FROM PADOVA

Sogus E.^{*}, Capece G., Petrosino A., Fornasier T., Riguzzi P., Mastellaro S., Caroli M., Bello L., Pegoraro E.
Department of Neurosciences, University of Padova, Padova, Italy

Spinal Muscular Atrophy (SMA) is a genetic motor neuron disease characterized by progressive muscle weakness and functional decline. The introduction of disease-modifying therapies (DMTs) has profoundly changed the natural history of SMA. While their short-term efficacy is established, data on the persistence of benefit over long-term follow-up in adult SMA patients remain limited.

The aim of this study was to evaluate whether DMTs are associated with sustained stabilization of motor function over time in a real-world adult SMA cohort. We performed a retrospective monocentric study including adult SMA patients followed at the Padova Neuromuscular Unit between 2018 and 2024. Clinical, genetic and longitudinal functional data were collected. Motor performance was assessed using validated scales (HFMSE and RULM). Patients were analyzed according to phenotype and treatment (nusinersen, risdiplam, both therapies in succession). Longitudinal trends were interpreted in light of natural history data.

56 patients were included (mean age 34.2 ± 14.5 years). 38 patients were treated with nusinersen, 18 with risdiplam; 6 patients switched from nusinersen to risdiplam. Across the cohort, HFMSE and RULM trajectories showed overall stabilization over follow-up, up to 90 months for nusinersen-treated patients. Stabilization was observed across all phenotypes. Switchers maintained previously achieved functional gains. Compared with natural history data, treated patients exhibited a milder functional decline than expected.

Adult SMA patients treated with nusinersen or risdiplam show stabilization of motor function over time, consistent across phenotypes. Functional stabilization represents a clinically meaningful outcome in adult SMA and supports the long-term value of DMTs in real-world settings.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143359

DNA METHYLATION IN PERIPHERAL BLOOD AS A NEW POTENTIAL BIOMARKERS SMA

Polito F.¹, Gasparo I.¹, Licitri L.¹, Drago S.F.², Romano S.¹, Torre A.¹, Gaouzi Z.¹, Panicucci C.³, Lo Cascio G.¹, Traverso M.³, Sframeli M.¹, Mirabello A.¹, Macaione V.¹, Errico F.⁵, Di Schiavi E.⁴, Corti S.⁶, Bruno C.³, Aguenouz M.^{*1}

¹ 1Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ² 2Department of Chemical, Biological, Pharmaceutical and Environmental Sciences, University of Messina, Messina, Italy, ³ 4Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health-DINOGMI, IRCCS Istituto Giannina Gaslini, University of Genoa, Genoa, Italy, ⁴ 5 Institute of Biosciences and Bioresources, IBBR Naples Division CNR, Napoli, Italy, ⁵ Ceinge Center University of Federico II Napoli, Napoli, Italy, ⁶ 3Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, SSD Neuromuscular and rare diseases, Milano, Milano, Italy

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease caused by impaired survival of the SMN (System Motor Neuron) protein, leading to the degeneration of motor neurons. Early diagnosis and reliable biomarkers are essential for disease monitoring and personalized treatment. However, epigenetic alterations may play a key role in disease severity/response to therapy, suggesting their involvement in the pathophysiology of the disease.

To highlight the effects of DNA methylation as an epigenetic alteration in peripheral blood DNA from patients with SMA, we studied a cohort of 37 samples using the bisulfite method followed by the Infinium MethylationEPIC BeadChip kit

The analysis identified 18 differentially methylated genes and re-

vealed an association between epigenetic alterations, SMA severity, and Rab/Rho GTPase signaling pathways. Specifically, the analysis showed differentially methylated genes in SMA patients compared to controls: these genes are involved in synaptogenesis, neuronal development, calcium signaling, epigenetic regulation, metabolism regulation, and cell proliferation. Other genes are involved in ion and nutrient homeostasis, and neuronal signaling. This preliminary study identifies distinctive DNA methylation signatures in SMA patients, suggesting a significant role for epigenetic dysregulation in disease mechanisms and biomarker discovery. Further studies are needed to clarify their functional impact.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143472

RESPIRATORY FUNCTION IN ADULT SMA PATIENTS AFTER LONG-TERM RISDIPLAM TREATMENT: THE EXPERIENCE OF ITALIAN CENTERS

Sframeli M.^{*1}, Materia R.¹, Tilenni Scaglione R.¹, La Rosa E.¹, Said I.¹, Trucco F.², Brolatti N.³, Coratti G.⁴, Albamonte E.⁵, Coccia M.⁶, Filosto M.⁷, Patanella A.K.⁸, Catteruccia M.⁹, Not R.¹⁰, Bruno I.¹¹, Maggi L.¹², Ricci F.¹³, Previtali S.¹⁴, Trabacca A.¹⁵, Vacchiano V.¹⁶, Pegoraro E.¹⁷, Agosto C.¹⁸, Mongini T.¹⁹, D'Amico A.⁹, Sansone V.⁵, Pane M.²⁰, Bruno C.²¹, Mercuri E.⁴, Messina S.A.I.W.G.¹

¹ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy, ² Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy, Genoa, Italy, ³ Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Italy, Genoa, Italy, ⁴ Pediatric Neurology, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Rome, Italy, Rome, Italy, ⁵ The NEMO Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Italy, Milano, Italy, ⁶ Department of Neurological Sciences, AOU Ospedali Riuniti di Ancona, Torrette, Ancona, Italy, Ancona, Italy, ⁷ Department of Clinical and Experimental Sciences, University of Brescia (Italy), NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, Brescia, Italy, ⁸ NeMO Center Armida Barelli, Fondazione Policlinico Universitario Agostino Gemelli, Rome, Italy, Roma, Italy, ⁹ Department of Neurosciences, Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, Roma, Italy, ¹⁰ Pediatric Neuromuscular Unit, Pediatric Neuropsychiatry Complex Unit, IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy, Bologna, Italy, ¹¹ Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, Trieste, Italy, ¹² Neuroimmunology and Neuromuscular Disease Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, Milano, Italy, ¹³ SC Neuropsichiatria Infantile, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy, Torino, Italy, ¹⁴ Neuromuscular Repair Unit, Institute of Experimental Neurology, IRCCS Ospedale San Raffaele, Milan, Italy, Milano, Italy, ¹⁵ Unit for Severe Disabilities in Developmental Age and Young Adults, Scientific Institute, IRCCS E. Medea, Brindisi, Italy, Brindisi, Italy, ¹⁶ IRCCS Istituto Delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy, Bologna, Italy, ¹⁷ Neurology Unit, Azienda Ospedale Padova, Padua, Italy, Padova, Italy, ¹⁸ Padua University Hospital, Padua, Italy, Padova, Italy, ¹⁹ Department of Neurosciences Rita Levi Montalcini, University of Turin, Turin, Italy, Torino, Italy, ²⁰ Centro Clinico NeMO, Fondazione Agostino Gemelli IRCCS, Rome, Italy, Roma, Italy, ²¹ Department of Neurosciences,

Rehabilitation, Ophthalmology, Genetics, University of Genoa, Genoa, Italy, Genoa, Italy

Spinal muscular atrophy (SMA) is characterized by progressive respiratory impairment, including in later-onset forms. The effects of treatments on respiratory function remain largely unexplored in large cohorts.

This study aimed to describe changes in respiratory function tests—including Forced Vital Capacity (FVC), FVC percent predicted (FVC%), Peak expiratory flow (PEF), PEF percent predicted (PEF%)—and motor function in adult SMA patients (aged ≥ 16 years) treated with risdiplam for more than 4 years.

Among 125 adult SMA patients with available respiratory data in the ITASMAC registry, long-term follow-up (> 4 years) was available for 68 patients, who constituted the study cohort (mean age 27.2 years, range 16–65; 49 SMA2 [72%], 19 SMA3 [28%]; 54.4% sitters, 38.2% non-sitters, 7.4% walkers). Hammersmith Functional Motor Scale Expanded score was ≤ 8 in 52/68 patients and did not change significantly after treatment ($p = 0.39$).

Mean FVC increased significantly from 1.59 ± 1.06 L (mean $\pm$ SD) at baseline to 1.72 ± 1.12 L after a mean follow-up of 5.3 years ($p = 0.007$). Instead, FVC% remained stable (median [IQR] 42 [29–64]% vs 42 [28–64]%; $p = 0.668$). PEF, assessed in a limited subset, improved significantly both in absolute values (3.44 ± 1.71 L vs 3.57 ± 2.44 L; $p = 0.0043$) and as PEF% (42 [21.75–70.25]% vs 50.5 [30.25–75.75]%; $p = 0.048$), reflecting improved expiratory airflow.

These data provide long-term respiratory follow-up in treated adult SMA patients and, for the first time, show improvement in commonly used pulmonary function tests, in contrast to motor outcomes. Therefore, FVC—and potentially also PEF—may be highly responsive, particularly in severely affected patients in whom motor scales might not detect changes.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143061

SMACK! PROJECT: IMPACT OF THE PARENT-CHILD INTERACTION IN THE EARLY NEURODEVELOPMENTAL STAGES OF A COHORT OF CHILDREN WITH SMA DIAGNOSED BY NEONATAL SCREENING – A PILOT STUDY

Parravicini S.^{*1}, Provera A.², Dosi C.¹, Zampini L.³, Masson R.¹, Provenzi L.²

¹ Fondazione IRCCS Istituto Neurologico “C. Besta”, Milano, Italy, ² IRCCS Fondazione Mondino, Pavia, Italy, ³ Università degli studi di Milano-Bicocca, Milano, Italy

The recent advent of disease-modifying therapies (nusinersen, risdiplam, onasemnogene APOB-related protein 1) has radically changed the disease trajectory of SMA. In parallel, the widespread adoption of neonatal screening has enabled early diagnosis, including pre-symptomatic stages, allowing prompt therapeutic interventions. These advances raise new questions regarding the role of early parent-child interactions and the impact of diagnosis-related medicalization on

neurodevelopment. Literature is scarce on the influence of caregiver-child relational dynamics in SMA, despite their potential relevance for clinical outcomes and family well-being.

this pilot study aimed to investigate early parent-infant interactions in children with SMA diagnosed via neonatal screening, compared with typically developing peers. We focused on interactional patterns across the first year of life, assessing the influence of maternal sensitivity, infant socio-emotional regulation, communicative development, and socio-cognitive responses. A further objective was to explore the psychological impact of diagnostic communication and subsequent medicalization on parental experience and dyadic exchanges.

The study enrolled SMA infants and controls, tested at 8-10-12 months. Preliminary findings suggest distinctive features of early parent-infant interactions in SMA, with potential modulation by maternal affective states and stress. Data indicate that the experience of diagnosis and medicalization can shape family dynamics and relational patterns, even in pre-symptomatic children who develop comparably to healthy peers.

In the era of neonatal screening and early therapeutic intervention, understanding the nuances of parent-child interaction is essential to optimizing care in SMA. This study highlights the need to integrate psychosocial and relational dimensions into clinical practice, aiming to support both neurodevelopmental outcomes and family well-being.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 143156

POLYGRAPHIC ASSESSMENT OF ADULT PATIENTS WITH SPINAL MUSCULAR ATROPHY FOLLOWING 12 MONTHS OF RISDIPLAM

Crescimanno G.¹, Rini N.^{*1}, Tomasello V.¹, Alonge P.¹, Di Stefano V.¹, Brighina F.¹, Marrone O.²

¹ Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy, ² National Research Council, Institute of Biomedical Research and Innovation (IRIB-CNR), Palermo, Italy

Investigations into the effects of risdiplam therapy in adult patients with spinal muscular atrophy (SMA) have mainly focused on diurnal respiratory parameters and motor outcomes. However, its potential impact on nocturnal respiratory events and autonomic regulation remains insufficiently explored.

To evaluate the effects of 12 months of risdiplam therapy on nocturnal respiratory function and autonomic activity in adult patients with SMA types 2 and 3.

Sixteen patients aged ≥ 16 years were assessed at baseline and after 12 months of treatment. Nocturnal cardiorespiratory polygraphy demonstrated a significant reduction in the Apnoea-Hypopnoea Index (AHI) and Oxygen Desaturation Index (ODI) ($p = 0.02$), whereas the time spent with oxygen saturation below 90% and the nadir oxygen saturation remained unchanged. Heart rate variability analysis showed a significant decrease in the SD2/SD1 ratio ($p = 0.03$), indicative of modified sympathovagal balance. Motor outcomes, measured using the Revised Upper Limb Module (RULM) and the Hammer-smith Functional Motor Scale Expanded (HFMSSE), exhibited modest improvements. Notably, changes in the SD2/SD1 ratio correlated with

variations in AHI but were not associated with motor scale changes. Risdiplam therapy in adults with SMA appears to be associated with improvements in nocturnal respiratory parameters alongside measurable changes in autonomic function. The observed reduction in sleep-related respiratory events may contribute to a more favorable autonomic profile.

FRIDAY, MAY 15TH, 2026

11:00-12:30

ORAL COMMUNICATIONS SESSION N.11

Modular Parallel Room 3

Chairs: Marcello Romano, Veria Vacchiano

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract Cod. 142781

REFINING ELECTROPHYSIOLOGICAL CRITERIA IN CIDP AND MMN: TOWARD A UNIFIED DEFINITION OF MOTOR CONDUCTION BLOCK AND PROXIMAL TEMPORAL DISPERSION

Gallo C.^{*1}, Fasano C.², Fonseca A.³, Falzone Y.⁴, Cocito D.⁵, Manganelli F.⁶, Matà S.⁷, Cosentino G.⁸, Di Stefano V.⁹, Filosto M.¹⁰, Leonardi L.¹¹, Ricciardi D.¹², Mazzeo A.¹³, Benedetti L.¹⁴, Luigetti M.¹⁵, Solla P.¹⁶, Inghilleri M.¹⁷, Habetswallner F.¹², Barilaro A.², Canale F.⁶, De Lorenzo A.¹, Ratti A.⁴, Cassano E.⁶, Spalletti M.⁷, Vegezzi E.¹⁸, Brighina F.⁹, Risi B.¹⁰, Forcina F.¹¹, Fasolino A.¹², Gentile L.¹³, Iabichella G.¹³, Beronio A.¹⁴, Vitali F.¹⁹, Moret F.¹⁷, Gazzina S.²⁰, Cabona C.²¹, Todisco V.²², Nobile--Orazio E.¹, Doneddu P.¹

¹ Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano, Milan, Italy, ² Department of Neuroscience and Sense Organs, Careggi University Hospital, Firenze, Italy, ³ Department of Neurology, Hospital Pedro Hispano, ULS Matosinhos, Portugal, ⁴ Division of Neuroscience, Department of Neurology, Institute of Experimental Neurology (INSPE), San Raffaele Scientific Institute, Milan, Italy, ⁵ Dipartimento Scienze Cliniche e Biologiche, Università di Torino, Turin, Italy, ⁶ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University Federico II, Naples, Italy, ⁷ Department of Neurological and Psychiatric Sciences, Azienda Ospedaliero-Universitaria di Careggi, Florence, Italy, ⁸ Department of Brain and Behavioral Sciences, University of Pavia, IRCCS Mondino Foundation, Pavia, Italy, ⁹ Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, 90127, Italy, ¹⁰ Department of Clinical and Experimental Sciences, University of Brescia; NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ¹¹ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ¹² Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy, ¹³ Department of Clinical and Experimental Medicine, Unit of Neurology, University of Messina, Messina, Italy, ¹⁴ U.O Neurologia, Ospedale Sant'Andrea, La Spezia, Italy, ¹⁵ Fondazione

Policlinico Universitario Agostino Gemelli IRCCS. UOC Neurologia, Rome, Italy, ¹⁶ Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy, ¹⁷ Department of Human Neurosciences, Rare Neuromuscular Diseases Centre, Sapienza University of Rome, Rome, Italy, ¹⁸ IRCCS Mondino Foundation, Pavia, Italy, ¹⁹ Università Cattolica del Sacro Cuore. Sede di Roma, Rome, Italy, ²⁰ Unit of Neurophysiology, ASST Spedali Civil, Brescia, Italy, ²¹ Division of Clinical Neurophysiology and Epilepsy Center, IRCCS Ospedale Policlinico San Martino, Genoa, Italy, ²² Division of Neurology and Neurophysiopathology, Department of Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy

The definition of motor conduction block (CB) and proximal temporal dispersion (TD) for the diagnosis of CIDP and MMN remains debated, particularly regarding whether CB should be based on amplitude or area reduction, and whether proximal TD is best assessed using negative peak or total CMAP duration.

Nerve conduction waveforms from 106 CIDP, 87 MMN, and 234 controls were analyzed. Motor CB was defined by $\geq 30\%$, $\geq 40\%$, or $\geq 50\%$ amplitude or area reduction. Proximal TD was defined as a $\geq 30\%$ increase in negative peak duration, total CMAP duration, or either criterion. Sensitivity, specificity, and inter-rater reliability were analysed.

Across both CIDP and MMN, a $\geq 30\%$ reduction in CMAP amplitude showed diagnostic performance comparable to area-based CB definitions and outperformed higher cut-off values. Requiring CB in multiple nerves increased specificity but reduced sensitivity. For proximal TD, negative peak duration was the most robust single parameter. Total CMAP duration identified additional abnormalities and, when combined with negative peak duration, improved diagnostic sensitivity in both disorders while maintaining high specificity. Total CMAP duration demonstrated acceptable inter-rater reliability. CMAP morphology showed substantial overlap between CIDP and MMN and limited discriminatory value.

A $\geq 30\%$ reduction in CMAP amplitude can be used as a universal definition of motor CB in both CIDP and MMN, providing diagnostic performance comparable to area-based criteria with greater simplicity. In addition, proximal TD assessed using total CMAP duration may represent a complementary electrophysiological criterion in both disorders.

NEUROPHYSIOLOGY AND PAIN

Abstract Cod. 143177

SMALL FIBER DYSFUNCTION IN FIBROMYALGIA: A MULTIMODAL STUDY

Dell'Aversana D.^{*1}, Masciarelli F.¹, Vitale F.¹, Ciccarelli G.¹, Caporaso G.², Tozza S.¹, Provitera V.², Manganeli F.¹, Nolano M.¹

¹ Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples Federico II., Naples, Italy, ² Istituti Clinici Scientifici Maugeri IRCCS, Skin Biopsy Lab, Neurological Rehabilitation Unit of Telese Terme Institute., Telese Terme, Italy

Fibromyalgia (FMS) is characterized by widespread musculoskeletal pain associated with symptoms like depression, migraine and fatigue. A subset of FMS patients presents small fiber pathology.

This study compares small fiber dysfunction in FMS patients with

neuropathic pain and autonomic symptoms (FMS-SFN) versus pure small fiber neuropathy (SFN) patients.

30 FMS-SFN patients and 67 SFN patients underwent sensory and autonomic evaluation through the "Small-Fiber-Neuropathy-Symptoms-Inventory-Questionnaire" (SFN-SiQ), "Composite-Autonomic-Symptoms-Score" (COMPASS-31), Quantitative-Sensory-Testing (QST), cardiovascular reflexes, Sympathetic-Skin-Response (SSR) and Dynamic Sweat Test (DST). Cutaneous innervation was analysed on punch biopsies from three body sites applying indirect Immunofluorescence procedures.

Compared to SFN patients (46 female, age 46+/-16), FMS-SFN (27 female, age 41+/-13) more frequently reported endometriosis (13% vs 1%), headaches (77% vs 16%) and depression (47% vs 7%). Dysimmune causes affected 47% of FMS-SFN and 36% of SFN patients, who had more glucose metabolism disorders (3% vs. 15%). FMS-SFN patients complained diffuse neuropathic pain, alongside more severe sensory and autonomic symptoms. Abnormal sensory thresholds were present in both groups with higher frequency of heat hyperalgesia in FMS-SFN (17% vs 1%) and higher thermal hypoesthesia at distal sites in SFN.

FMS-SFN patients presented a lower RR variability at rest and non-length-dependent hypohidrosis with lower sweat volume per gland at proximal sites. Cutaneous sensory and autonomic innervation did not differ between the two groups.

FMS-SFN patients had a non-length-dependent SFN with a more diffuse neuropathic pain and more severe autonomic symptoms. They, also, presented a mild cardiovascular parasympathetic impairment and a proximal lower sweat production per gland. Skin biopsies did not differentiate the two groups.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract Cod. 142986

NEUROPHYSIOLOGICAL ASSESSMENT IN PATIENTS WITH SPINAL MUSCULAR ATROPHY IDENTIFIED BY NEWBORN SCREENING

Masson R.^{*}, Cazzato D., Dosi C., Parravicini S., Zanin R., Arnoldi M.T., Gellera C., Venerando A., Lanteri P.

Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy

In spinal muscular atrophy (SMA), disease-modifying treatments are highly effective when administered prior to symptom onset, prompting the implementation of newborn screening (NBS) programs in a growing number of countries. In this study, we aimed to assess the role of neurophysiological assessment in presymptomatic patients identified through NBS program, in whom prognosis cannot be inferred from clinical evaluation alone.

This was a single-center prospective cohort study of 12 consecutive infants with SMA (≤ 3 survival motor neuron 2 [SMN2] copies) identified through the Lombardy NBS program between September 2023 and December 2025. Clinical and motor function scores (CHOP-INTEND scale), genetic and neurophysiological data were collected. The neurophysiological protocol consisted of compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) of

the median and ulnar nerves for the upper limbs; the medial plantar, tibial, and peroneal nerves for the lower limbs; F-wave studies; and motor unit number estimation (MUNE).

Twelve patients with 2 or 3 SMN2 copies were assessed at baseline, and followed up at 3, 6, and 12 months after treatment. Even within the neonatal window, motor unit indices (MUNE/SMUP) and CMAP values showed meaningful correlations with CHOP-INTEND scores. The pTA CMAP appeared particularly sensitive to genotype (SMN2 copy number). Infants who initiated treatment earlier exhibited better-preserved CMAP and MUNE values, even when matched for age.

These findings support the concept that presymptomatic therapy attenuates early motor neuron loss. Children treated earlier maintain the greatest advantage, with higher CMAP amplitudes, higher CHOP-INTEND scores, and more stable F-wave persistence.

NEUROPHYSIOLOGY AND PAIN

Abstract Cod. 143372

LONG-TERM OUTCOMES AND NATURAL HISTORY OF SMALL FIBER NEUROPATHY

Devigili G.^{*1}, Lombardi R.², Marchi M.², Mehmeti E.³, Dalla Bella E.², Riva N.², Cazzato D.⁴, D'Amato I.², Giordano A.², Cartelli D.², Salvi E.³, Lauria G.⁵

¹ Movement Disorders Unit, Clinical neurophysiology Unit, Fondazione IRCCS Istituto Neurologico, Milano, Italy, ² Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³ Data Science Center, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ⁴ Neurophysiology Unit, Fondazione IRCCS Istituto Neurologico, Milan, Italy, ⁵ Fondazione IRCCS Istituto Neurologico Carlo Besta, Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy, Milano, Italy

Small Fiber Neuropathy (SFN) is a complex disorder characterized by neuropathic pain, and dysautonomia. It is associated with several etiologies, although many cases remain idiopathic. The natural history of SFN is poorly defined.

To characterize the clinical features of patients with SFN across different etiologies, assess therapeutic responses, and evaluate whether longitudinal follow-up data can refine etiological diagnoses and prognostic stratification.

The cohort study with retrospective baseline and prospective reassessment included patients with SFN who had undergone a standardized baseline evaluation, including clinical assessment, pain questionnaires, nerve conduction studies, quantitative sensory testing, and skin biopsy with measurement of intraepidermal nerve fiber density. Participants also underwent etiological screening reassessment, treatment response evaluation, and skin biopsy. A total of 178 patients were included; 76 underwent a second skin biopsy. Etiologies were classified as immune-mediated (17.4%), metabolic (18.5%), toxic (6.7%), genetic (12.9%), or cryptogenic (44.4%). Over time, 32 patients developed large fiber involvement. Clinical outcomes were heterogeneous: 21 patients with treatable etiologies showed partial or complete recovery. Of the 79 cryptogenic patients, 34 remained stable, while etiological diagnoses changed over time in 14. Patients with subacute-onset SFN achieved complete clinical

recovery within one year, whereas others experienced relapses with persistent skin denervation. Symptomatic treatment led to a $\geq 50\%$ reduction in NRS pain in 38% of patients.

Our preliminary findings suggest that the outcome of SFN is largely dependent on etiology. Treatable forms can recover, whereas cryptogenic cases are often stable but rarely reversible. Subacute-onset SFN appears as a distinct and potentially reversible phenotype.

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Abstract Cod. 143519

DISEASE MODELLING IN DUCHENNE MUSCULAR DYSTROPHY – SINGLE-CENTRE PILOT STUDY USING A MACHINE LEARNING APPROACH

Trucco F.^{*1}, Morando S.², Roascio M.³, Scotto C.³, Latinakis G.², Gizzi G.⁴, Panicucci C.², Brolatti N.⁴, Pedemonte M.⁴, Striano P.¹, Bruno C.⁵, Arnulfo G.³

¹ 1 Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa 2 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy, ² 3 Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy, ³ 4 Department of Computer Science, Bioengineering, Robotics and Systems Engineering, University of Genoa, Genoa, Italy, ⁴ 1 Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy, ⁵ 2 Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa 3 Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy

Duchenne muscular dystrophy (DMD) is a multifaceted disorder. Current longitudinal models do not fully capture the differential progression toward disease milestones, impacting on clinical care and translational research.

To develop a predictive model based on machine learning algorithm to characterise, in a single-centre longitudinal natural history cohort, the influence of variables associated with the loss of ambulation (LoA).

The model was applied to ambulant DMD patients followed by our Centre (2020-2025), treated with corticosteroids and with ≥ 2 visits. LoA was defined as the main outcome. Disease models were compared between those who remained ambulant vs those who lost ambulation throughout study period.

Leaspy framework was used to model the population-level disease trajectory based on i.Forced Vital Capacity, ii.North Star Ambulatory Assessment, iii.Rise-from-Floor. Upon normalization, the model estimated, for each patient, a time shift (τ , time-to-disease start) and an acceleration factor (γ , progression rate).

Data from 58 DMD was included, mean age at first visit was 5.8(± 2.9) years, average follow-up 11.2 years. The age at last available visit in those who maintained ambulation and the age at LoA in those becoming non-ambulant did not differ ($p = 0.1$).

The model captured disease progression satisfactorily (mean absolute error ≈ 0.1). Disease duration prior to the decline (τ) did not differ between groups ($p \approx 0.68$), but once the decline started,

all three functional measures progressed faster in those who lost ambulation ($p \approx 0.026$).

This preliminary model provides novel insights on DMD disease milestones and offers personalized progression profiles. Further work is ongoing to refine the model accounting for clinical and genetic variables, and to extend it to broader DMD cohorts.

GENETIC NEUROPATHIES

Abstract Cod. 143439

ELECTROPHYSIOLOGICAL EVIDENCE OF PRECLINICAL NON-LENGTH DEPENDENT SENSORY INVOLVEMENT IN TTR AMYLOIDOSIS

Castiglia M.^{*1}, Aiello A.¹, Fiumarella R.¹, Dell'Aversana D.¹, Cassano E.², Canale F.³, Nolano M.¹, Manganelli F.¹, Tozza S.¹

¹ Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples Federico II, Naples, Italy., Naples, Italy,

² Neurology Unit, Ospedale del Mare, Naples, Italy., Naples, Italy,

³ Neurology Unit, University Hospital Federico II, Naples, Italy., Naples, Italy

Hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) is a rare and disabling disease. Pathogenesis is not fully understood; the prevailing hypothesis suggests early amyloid deposition in dorsal root ganglia, leading to sensory neuron dying-back degeneration. This study aimed to investigate preclinical ganglionopathy in ATTRv carriers using an electrophysiological marker of non-length dependent neuropathy.

Presymptomatic ATTRv subjects followed at the University of Naples were recruited. Clinical data included age, gender, predicted age of disease onset (PADO) and time-to-PADO. Sensory action potential (SAP) amplitudes of radial and sural nerves were recorded, and the sural/radial ratio (SRR) was calculated to assess non-length dependent neuropathy.

Twenty-eight genetically confirmed ATTRv carriers were enrolled (46.4% male; mean age 56.6 ± 14.3 years). Mean PADO was 63.5 ± 6.2 years and mean time-to-PADO was 12.6 ± 14.5 years. Radial and sural SAP amplitudes were within normal limits.

A one-sample Wilcoxon signed-rank test was conducted to examine whether the median SRR (Median = 0.47; IQR = 0.391, 0.821) differed from the theoretical value (0.21). Results indicated a statistically significant difference ($Z = -4.17$, $p < .001$) with a very large effect size ($r = .79$). SRR did not differ by gender ($p = 0.072$) or mutation type ($p = 0.057$) and did not correlate with PADO ($p = 0.201$) and time-to-PADO ($p = 0.681$).

In ATTRv carriers, SRR was abnormal despite normal SAP, suggesting early non-length dependent sensory involvement, independently of PADO. SRR could therefore be a useful tool for detecting early sensory involvement in ATTRv presymptomatic subjects, potentially contributing to earlier disease monitoring and stratification.

THURSDAY, MAY 14TH, 2026

15:00-16:30

POSTER SESSION MYASTHENIA | odd numbers

Chairs: Silvia De Pasqua, Anna Fetta

MYASTHENIA

Abstract P057 - Cod. 143346

A SINGLE-CENTER REAL-WORLD EXPERIENCE OF EFGARTIGIMOD IN ANTI-ACHR-POSITIVE GENERALIZED MYASTHENIA GRAVIS

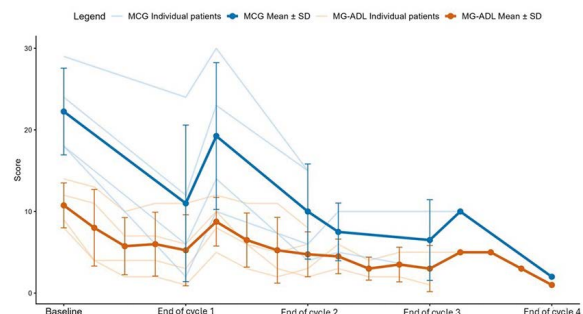
Iusi I.C.^{*1}, Marino L.¹, Sirgiovanni S.¹, Serra F.¹, Lucchino R.¹, Perri B.¹, Bruno P.A.¹, Zoleo P.², Barone S.², Valentino P.¹, Gambardella A.¹, Trimboli M.²

¹ Institute of Neurology, Department of Medical and Surgical Sciences, "Magna Græcia" University, Catanzaro, Italy, ² Neurology Unit, AOU "Renato Dulbecco", Catanzaro, Italy

Efgartigimod is an FcRn antagonist approved for the treatment of anti-acetylcholine receptor (AChR) antibody-positive generalized myasthenia gravis (gMG). Real-world data on its long-term efficacy and impact on patient-reported outcomes remain limited.

This single-center retrospective study, conducted at the outpatient neuromuscular clinic of Catanzaro, aimed to evaluate the long-term efficacy and safety of Efgartigimod. Five patients with confirmed anti-AChR-positive gMG were treated with intravenous or subcutaneous Efgartigimod according to clinical indications. Clinical efficacy was assessed using MG-ADL and QMG scores at baseline and across successive treatment cycles. Fatigue and quality of life were evaluated using FSS and MG-QoL15r at baseline, 6, and 12 months. One patient discontinued treatment due to lack of efficacy and was excluded from the final analysis.

Four patients (4 female, mean age: 58.25 ± 24.78 years) completed a one-year follow-up. Mean MG-ADL scores improved from 10.8 ± 2.8 at baseline to 4.0 ± 3.6 , with a mean reduction of 6.8 points. QMG scores decreased from a mean baseline value of 22.3 ± 5.3 to



8.8 ± 7.2 after repeated treatment cycles. While FSS scores showed only a slight improvement, MG-QoL15r scores exhibited a reduction from 19.0 ± 4.7 to 13.4 ± 3.8 at 12 months. No treatment-related adverse events were reported.

In this small real-world cohort of anti-AChR-positive gMG patients, Efgartigimod was effective and well tolerated, with sustained improvements in clinical and patient-reported outcomes. Although statistical significance was limited by sample size, consistent trends support its favorable efficacy and safety profile in routine clinical practice.

MYASTHENIA

Abstract P061 - Cod. 143371

ANTI-COMPLEMENT THERAPY IN MYASTHENIA GRAVIS: A SINGLE CENTER REAL LIFE EXPERIENCE

Della Valle P.*, Erra C., Ricciardi D., Fasolino A., Matrone F., Tuccillo F., Habetswallner F.
Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy., Napoli, Italy

Complement C5 inhibitors, including eculizumab, ravulizumab, and zilucoplan, have demonstrated efficacy and safety in phase 3 trials and real-world studies in anti-acetylcholine receptor-positive (AChR+) generalized myasthenia gravis (gMG).

This study aimed to evaluate the real-world effectiveness of C5 inhibitors in a single-center cohort and to describe clinical outcomes in patients switching from eculizumab to ravulizumab.

We performed a retrospective analysis of gMG patients treated with C5 inhibitors at Cardarelli Hospital (Naples) between November 2022 and May 2025. Clinical assessments using the Myasthenia Gravis Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales were conducted at 1, 3, 6, 12, and 24 months. Outcomes included responder rates (MG-ADL reduction ≥3 points), changes in concomitant immunosuppressive therapies, and the number of disease exacerbations requiring rescue treatment.

Forty-four patients were included: 27 received eculizumab, 12 ravulizumab, and 5 zilucoplan. Sixteen patients switched from eculizumab to ravulizumab after a mean treatment duration of 15.8 months. All treatments led to a significant reduction in MG-ADL and QMG scores at all timepoints compared with baseline ($p < 0.001$). At last follow-up, responder rates were 86% for eculizumab, 84% for ravulizumab, and 100% for zilucoplan. Prednisone tapering was achieved in 82%, 75%, and 100% of patients, respectively. In the switch group, clinical stability was maintained in 92% of patients, with good tolerability. In real world practice, C5 inhibitors were effective, improved symptoms, and showed a steroid sparing effect.

MYASTHENIA

Abstract P063 - Cod. 143366

ANTIBODY DETECTION IN TREATED MYASTHENIA GRAVIS: COMPARING ELISA

AND CELL-BASED ASSAYS

Serra L.*¹, Ricciardiello F.¹, Grondona A.G.², De Pasqua S.¹, Gligora I.⁵, Morelli L.¹, Fetta A.³, Donadio V.A.⁴, Liguori R.⁴, Giannoccaro M.P.⁴

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy,

² LUM Autoimmunità e Allergologia, Ospedale Maggiore, Bologna, Italy,

³ Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università di Bologna; IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età Pediatrica, Ospedale Sant'Orsola-Malpighi, Bologna, Italy, ⁴ IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica; Dipartimento di Scienze Biomediche e Neuromotorie (DIBINEM), Università di Bologna, Bologna, Italy, ⁵ Dipartimento di Scienze Biomediche e Neuromotorie (DIBINEM), Università di Bologna, Bologna, Italy

Myasthenia gravis (MG) is an autoimmune disorder in which antibodies target neuromuscular proteins, mainly acetylcholine receptors (AChR) and muscle-specific kinase (MuSK). While studies have compared diagnostic assays like enzyme-linked immunosorbent assay (ELISA) and cell-based assay (CBA), the impact of immunotherapy on their sensitivity remains unclear. Precise antibody detection is crucial for diagnosis, monitoring, and therapy guidance, making it essential to distinguish true seroreversion from test limitations.

We evaluated 85 MG patients undergoing immunotherapy (63 generalized-MG, 22 ocular-MG, mean age 63,44±17,87 years; M/F = 39/46) to assess antibody detection across assays. Sera were tested using ELISA, live-CBA (l-CBA), and fixed-CBA (f-CBA). Patients were classified as ever-negative (consistently radioimmunoassay-negative) or ever-positive (with previously documented antibodies). We collected demographic and clinical data, disease duration, treatment history, and antibody results, and then compared detection rates across assays by therapy type and duration.

Among treated patients, l-CBA detected antibodies in 69,4%, f-CBA in 67,1%, and ELISA in 63,5% ($p = 0,022$). Notably, 3 out of 20 ever-negative cases (15%) resulted l-CBA-positive during follow-up. In the 64 ever-positive treated patients, antibody positivity remained stable (l-CBA 85,9%, f-CBA 85,9%, ELISA 84,4%). Nine ever-positive patients lost both CBAs and ELISA reactivity, including 4 MuSK-Ab (3 on rituximab and 1 on IVIG/corticosteroids) and 5 AChR-Ab positive patients on corticosteroids; one additional AChR-Ab positive case on corticosteroid treatment tested negative by ELISA.

In most cases seropositivity persisted despite immunotherapy. Some patients who were ever-negative on standard tests resulted positive with l-CBA at follow-up, indicating that CBA may reveal previously undetectable antibodies even under treatment.

MYASTHENIA

Abstract P065 - Cod. 143076

AUTOIMMUNE COMORBIDITIES AS PROGNOSTIC DETERMINANTS IN THYMOMA-ASSOCIATED MYASTHENIA GRAVIS: EXPERIENCE FROM A SINGLE-CENTER COHORT

Habetswallner F.*, Falso S., Marini S., Marini M., Aulitto E., Iorio R.
Department of Neurosciences, Università Cattolica del Sacro Cuore, Rome, Italy, Rome, Italy

Thymoma-associated Myasthenia Gravis (TAMG) represents a clinical entity with poorer prognosis when compared to other MG subtypes. Outcome predictors are lacking. We conducted a retrospective study to identify clinical variables associated with favorable MG outcome as minimal manifestation or better according to MGFA post-intervention status (MGFA-PIS).

We retrieved information from clinical records of consecutive TAMG patients seen at our Institution between January 2005 and May 2025. Outcome predictors as patient demographics, MG severity (at onset and at maximum severity) and related treatment, and pathologic variables, thymoma stage (according to Masaoka classification) and histotypes (according to WHO classification) were assessed by univariate and multivariate analyses performed in R 4.3.1 Software Version.

A total of 118 patients [59 (50%) females, median age (IQR, years) = 63 (54-78)] with acetylcholine receptor antibody positive MG (AChR-MG), and histologically confirmed thymoma were included. The outcome was assessed by MGFA-PIS at the last follow-up. Fourteen cases were excluded either due to missing data or to follow-up period < 1 year. The univariate logistic regression revealed that the presence of autoimmune comorbidities (AIC) known or unknown to be linked to thymoma, and occurring at any time of patient history, was significantly associated with lower chances to achieve 'MM-or-better', OR 0.22 (95% CI, 0.08-0.72; $p = 0.006$). There were no significant differences in follow-up durations between patients with and without AICs

AICs can influence clinical outcome of patients with TAMG and should be carefully considered in therapeutic decision-making.

Univariate logistic regression (Outcome: MM or better)

Predictor	OR	95% CI	p
Male sex	2.65	1.23–5.87	0.014
Age at onset (years)	1.00	0.98–1.03	0.868
Late onset (50–65 years)	1.23	0.57–2.63	0.599
Very late onset (>65 years)	0.78	0.30–2.07	0.611
Autoimmune comorbidities	0.22	0.07–0.63	0.006
Thymoma-associated MG	1.00	0.25–3.52	0.996
MGFA class I at onset	2.18	0.96–5.28	0.071
MGFA III–V at onset	0.56	0.06–4.77	0.564
Thymectomy >6 months	1.21	0.54–2.72	0.641
IST start >6 months	0.61	0.24–1.56	0.302
Cortical histotype	1.24	0.48–3.12	0.652
Antibody positivity	0.63	0.22–1.83	0.389

MYASTHENIA

Abstract P067 - Cod. 143479

BALANCING IMMUNODEFICIENCY AND AUTOIMMUNITY: MANAGEMENT OF ANTI-MUSK MYASTHENIA GRAVIS IN AN HIV-POSITIVE PATIENT

Lo Iacono A.*, Cepele A., Iovino V., Guida M., Maestri Tassoni M.

Department of Experimental and Clinical Medicine, Neurology Unit, University of Pisa, Pisa, Italy

Autoimmune manifestations in patients with HIV infection have been described in association with immune reconstitution following the initiation of antiretroviral therapy. Myasthenia gravis(MG) is a rare manifestation in HIV-infected patients. Its observation highlights the complexity of the mechanisms governing the balance between immunodeficiency and autoimmunity in this population.

We describe a case of HIV-associated Myasthenia Gravis treated with Rituximab.

A 71-year-old male patient with HIV infection, diagnosed in 2004 and on stable antiretroviral treatment with dolutegravir and lamivudine, presented ocular and oropharyngeal symptoms. He was then diagnosed with generalized Myasthenia Gravis(MGFA class IIIB) associated with positive anti-MuSK antibodies in 2010 and treated with two courses of intravenous immunoglobulins. From 2010 to 2023, the disease remained clinically stable without the need for other treatment. In 2024, a severe worsening of oropharyngeal symptoms occurred(MG-ADL 8). The administration of rituximab was discussed with infectious disease specialists and after assessment of immune status through CD4+ lymphocyte monitoring and HIV-RNA dosage(absent). He underwent Rituximab administration in March 2024 and March 2025 and resulted in significant clinical improvement(MG-ADL 2). Antiretroviral treatment continued and no serious side effects have been reported.

To the best of our knowledge, only four cases of MuSK-MG with HIV infection have been described, usually related to immune reconstitution inflammatory syndrome. Treatment in these cases is challenging due to risk of infection reactivation during immunosuppressant therapy and the need of multidisciplinary approach. In this case, rituximab was effective and well tolerated, with no serious adverse events, likely reflecting good control of HIV infection.

MYASTHENIA

Abstract P069 - Cod. 142978

BEYOND FORCED VITAL CAPACITY: RESPIRATORY MUSCLE TESTING REVEALS HIDDEN DYSFUNCTION IN GENERALIZED MYASTHENIA GRAVIS

Maccora S.*, Crescimanno G., Di Marco R., Vitrano M., Mineo M., Brighina F., Di Stefano V.

Department of Biomedicine, Neuroscience, and Advanced Diagnostic (BIND), University of Palermo, Palermo, Italy

Respiratory dysfunction is a common and clinically relevant feature of myasthenia gravis, contributing to disease severity, reduced quality of life, and risk of myasthenic crisis. Assessment often relies on forced vital capacity (FVC), while more sensitive tests of respiratory muscle function, such as maximal inspiratory and expiratory pressures (MIP, MEP) or sniff nasal inspiratory pressure (SNIP), are available only in tertiary neuromuscular centers. The incidence of obstructive respiratory syndromes in gMG remains poorly defined.

This monocentric study included 79 patients with seropositive generalized MG (67 anti-AChR, 11 anti-MuSK, 1 anti-LRP4). Respiratory evaluation included clinical scales, dyspnea questionnaires, spirometry, respiratory muscle tests (MIP, MEP, SNIP), oscillometry, 6-minute walk test (6MWD), and arterial blood gas analysis.

Restrictive ventilatory patterns ($FVC < 80\%$) were observed in 34 patients (43%), mostly mild to moderate by QMG criteria. Obstructive patterns ($FEV1/FVC < 70\%$) occurred in 6 patients (7.6%), four with pre-existing asthma. FVC and MIP correlated with cough strength, inspiratory pressures, 6MWD, and quality of life. Regression analysis identified MIP and airway resistance (R5-19) as significant predictors of disease severity (MG-ADL, QMG), whereas FVC, MEP, and peak cough flow were less predictive.

In this mild-moderate gMG cohort, restrictive ventilatory patterns were frequent, and obstructive patterns were occasional, likely linked to asthma or pyridostigmine use. MIP better reflects disease severity, daily function, and quality of life than FVC or other respiratory tests. These findings support using MIP to detect respiratory dysfunction even outside myasthenic crisis.

MYASTHENIA

Abstract P071 - Cod. 143477

BEYOND MUSCLE WEAKNESS: A META-ANALYSIS OF COGNITIVE FUNCTION IN MYASTHENIA GRAVIS

Criante M.S.*¹, Mengoli E.¹, Vozzi S.², Zenesini C.¹, Vaioli G.¹, Succi A.¹, Donadio V.A.¹, Liguori R.¹, Fonti C.¹, Giannoccaro M.P.¹

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy,

² Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy

Cognitive impairment in myasthenia gravis (MG) has been increasingly recognized, yet its prevalence, pattern, and contributing factors remain unclear. This meta-analysis aims to provide a current overview of the association between myasthenia gravis, cognitive functioning, fatigue, and mood.

Following PRISMA guidelines (PROSPERO: CRD420251121809), PubMed and Scopus were searched through June 2025. Eligible studies included presence of a control group, ≥ 10 participants per arm, and extractable cognitive outcomes. Neuropsychological tests were classified into six domains and data were synthesized using random-effects models with Standardized Mean Differences (SMD). Thirteen case-control studies (435 patients, 328 controls) were eligible. MG patients showed significantly poorer performance across multiple cognitive domains. Moderate impairment was found in global cognition ($SMD = -0.42$). Verbal and visual memory defi-

cits were pronounced in immediate recall (verbal $SMD = -0.78$; visual $SMD = -0.76$) and remained significant for verbal delayed recall ($SMD = -0.68$). Executive-attentional functioning was reduced both in tasks with motor components (e.g., visuo-spatial search; $SMD = -0.50$) and without motor components (e.g., verbal fluency; $SMD = -0.56$). MG patients also exhibited higher levels of depression ($SMD = -0.94$) and anxiety ($SMD = -0.85$). Heterogeneity was high across domains (I^2 73.4–98.6%). All studies were rated poor quality.

MG patients show deficits across multiple cognitive domains, alongside prominent affective symptoms likely contributing to cognitive variability. However, heterogeneity and methodological limitations of available studies, hinder definitive conclusion. Future research should assess mood, fatigue, MG clinical subtypes, and treatment effects to clarify mechanisms underlying cognitive dysfunction in MG.

MYASTHENIA

Abstract P073 - Cod. 143295

CLINICAL AND NEUROPHYSIOLOGICAL FEATURES OF A TRIPLE AUTOIMMUNE OVERLAP: MYASTHENIA GRAVIS, MYOSITIS, AND GRAVES' DISEASE

Bavestrello G.*¹, Faedo E.¹, Barone C.¹, Vollaro A.F.M.¹, Cabona C.², Marinelli L.², Schenone A.¹, Grandis M.¹

¹ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy., Genoa, Italy, ² Electromyography and Intraoperative Neurophysiological Monitoring Unit, Neurophysiopathology Unit, IRCCS AOM Policlinico San Martino., Genova, Italy

The coexistence of Myasthenia Gravis (MG), inflammatory myopathies, and autoimmune thyroid disease constitutes a rare and complex clinical entity within the spectrum of multiple autoimmune syndromes. We report a case of this triple autoimmune overlap, highlighting the specific neurophysiological findings.

A 47-year-old woman with a prior history of thyroidectomy for Graves' disease presented with progressive proximal lower limb weakness and myalgia. Several months later, she developed fluctuating double vision. Laboratory testing revealed markedly elevated creatine kinase levels (peak 2954 U/L) and high-titer antinuclear antibodies (ANA 1:640). Serological evaluation confirmed the presence of anti-acetylcholine receptor (AChR) antibodies, while an extensive myositis-specific antibody panel, including anti-HMGCR, was negative. Whole-body MRI demonstrated diffuse muscle edema consistent with inflammatory myopathy, predominantly affecting the lower limbs. Imaging studies excluded thymoma.

Neurophysiological assessment provided key diagnostic insights. Repetitive Nerve Stimulation was normal. Concentric needle EMG demonstrated an early recruitment pattern of short-duration, and low-amplitude motor unit potentials (MUPs) associated with abundant spontaneous activity. Notably, neuromyotonic discharges and doublets were observed in distal muscles, coexisting with typical fibrillation potentials.

Treatment with corticosteroids led to normalization of muscle enzyme

levels and significant improvement in motor function, while ocular symptoms required the introduction of pyridostigmine and methotrexate.

This case illustrates the phenotypic variability of autoimmune neuromuscular overlap syndromes. The presence of neuromyotonic discharges in the context of AChR+ MG and seronegative myositis expands the spectrum of neurophysiological manifestations in these complex disorders, underscoring the importance of multimodal diagnostic assessment.

MYASTHENIA

Abstract P075 - Cod. 142900

CLINICAL CHARACTERISTICS, TREATMENT PATTERNS, AND FUNCTIONAL OUTCOMES IN EARLY-, LATE-, AND VERY LATE-ONSET MYASTHENIA GRAVIS: A RETROSPECTIVE OBSERVATIONAL STUDY

Camera G.^{*}, Paone P., Agazzi E., Sgarzi M.
ASST PAPA GIOVANNI XXIII, Bergamo, Italy

The mean age at onset of myasthenia gravis (MG) has markedly increased in recent decades, as consistently reported in the literature. This epidemiological shift may influence disease presentation, progression, and management, suggesting that the clinical course of MG should be re-evaluated to determine whether distinct patterns emerge across different age categories at onset.

We aimed to describe clinical features, treatment patterns, and functional outcomes by early- (< 50 y), late-, and very-late-onset MG (> 65 y). We conducted a retrospective study identifying patients through a hierarchical three-cohort approach using exemption codes, ICD-9/10 diagnoses, and MG-specific treatments, comparing onset severity, antibody status, therapies, and outcomes across age groups. Among 285 patients, MG severity at onset differed significantly between groups ($p = 0.0021$), with EO-MG showing a distinct distribution compared to LO-MG and VLO-MG (Fig. 1). AChR serological status also varied ($p = 0.001$), with higher seronegativity in EO-MG (37.7%) compared to LO-MG (25.3%) and VLO-MG (12.7%). Anti-

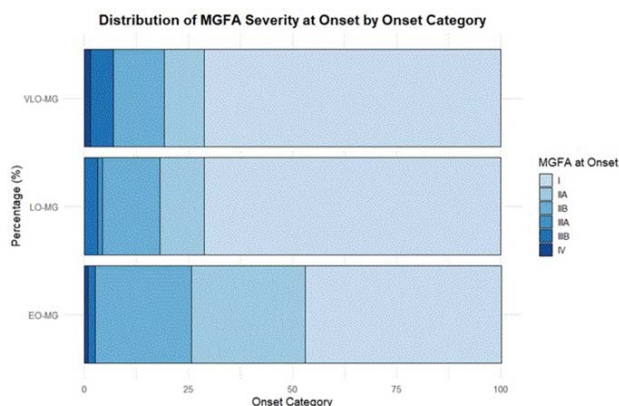


Fig. 1: Stacked bar chart showing the percentage of patients in each MGFA severity class at disease onset for Early Onset (EO-MG), Late Onset (LO-MG), and Very Late Onset (VLO-MG). The MGFA severity classes are represented by different shades of blue, ranging from light blue (I) to dark blue (IV).

body titers tended to be lower in VLO-MG, approaching statistical significance after adjustment ($p = 0.053$). Pyridostigmine was the most commonly used treatment. Triple therapy differed significantly between groups, favoring EO-MG ($p = 0.033$). Coexisting autoimmune diseases were associated with an increased risk of clinical worsening (OR 2.77, $p = 0.018$), while hypertension was linked to greater deterioration in activities of daily living (+1.88 points, $p = 0.032$). Functional outcomes at last follow-up were comparable across groups ($p = 0.28$).

Age at onset influences MG severity, serological profile, and treatment strategies, while long-term functional outcomes appear similar across groups. Comorbid autoimmune conditions may predict clinical worsening.

MYASTHENIA

Abstract P077 - Cod. 142792

CLINICAL FINDINGS, TREATMENT RESPONSE AND LONG-TERM OUTCOME IN JUVENILE MYASTHENIA GRAVIS

Moroni I.^{*1}, Penzo M.¹, Segre G.¹, Cazzato D.², Mikael Gian Andrea I.², Antozzi C.³, Danti F.R.¹

¹ Department of Pediatric Neurosciences, FONDAZIONE IRCCS ISTITUTO NEUROLOGICO CARLO BESTA, Milan, Italy, ² Neurophysiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³ Neuroimmunology and Neuromuscular Disease Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Juvenile myasthenia gravis (JMG) presents with onset before 18 years of age, with purely ocular form (OMG) or generalized muscle involvement (gMG). Given the rarity of the disease in childhood there is a limited number of studies on large series of JMG patients and evidence-based guidelines for diagnosis and management are still lacking. This study aims to provide an in-depth clinical characterization of a large monocentric series of JMG patients.

An observational, monocentric, retrospective cohort study. Relevant demographic, clinical, neurophysiological and serological data of 49 patients that were diagnosed and followed up over the last 20 years were collected and analyzed.

Of 18 OMG patients (mean age at onset 8 ± 4.2 years), 50% were AChR antibody positive. Repetitive nerve stimulation (RNS) demonstrated significant decrement in 60% of tested cases. Treatment included mainly pyridostigmine (Py) and glucocorticoids (GC). Complete stable remission or pharmacological remission was achieved in 3 patients (18%) at last follow-up.

Among 31 gMG patients (mean age at onset 9.7 ± 4.2 years), 58% were AChR antibody positive, 22% MuSK positive, and 19 % seronegative. Almost half presented with bulbar signs; RNS showed decrement in 87%. First line treatment mostly included Py, GC, and IVIg; some patients required immunosuppressants or plasmapheresis. Overall 25% of gMG patients presented with treatment-refractory JMG; 2 patients have been treated with Rozanolizumab and Ravulizumab respectively with significant benefit at present, that allowed us to reduce/interrupt GC.

Treatment-refractory juvenile gMG represents a significant ongoing

challenge, highlighting an unmet need for effective and well-tolerated new therapies in the pediatric population.

MYASTHENIA

Abstract P079 - Cod. 142940

COGNITIVE DYSFUNCTION AND QUANTITATIVE EEG FINDINGS IN MYASTHENIA GRAVIS PATIENTS

Meli A.*, Bacile E., Patitucci G., Lima S.M., Di Martino G., D'Amico F., Quartetti U., Rini N., Labate A., Brighina F., Di Stefano V.
Biomedicine, Neuroscience and Advanced Diagnostic (Bi.N.D.) Department, University of Palermo, Palermo, Italy

Myasthenia gravis (MG) is a rare autoimmune disorder characterized by autoantibodies directed against specific proteins at the neuromuscular junction. Although traditionally regarded as a purely peripheral nervous system disorder, growing evidence indicates that a subset of patients may also display cognitive and neuropsychiatric manifestations.

This study aimed to evaluate cognitive functioning in patients with MG and its potential correlation with quantitative electroencephalography (qEEG) measures. Twenty-five patients with MG followed at the Center for Rare Diseases of the A.O.U.P. of Palermo were enrolled. EEG was recorded and analyzed using EEGLAB software. Spectral power in the 2–30 Hz frequency range was computed and quantitative data were extracted. Subsequently, participants underwent a neuropsychological assessment, which included the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Hospital Anxiety and Depression Scale (HADS), Myasthenia Gravis Quality of Life 15-item revised scale (MG-QOL15r), Fatigue Severity Scale (FSS) and the Neuro-QoL Fatigue Short Form. Finally, Pearson's correlation analyses were used to assess associations between qEEG parameters and clinical scores.

We observed a positive correlation between increased power in slow frequency bands (theta and delta) and lower scores on the neuropsychological battery, along with a corresponding reduction in alpha power.

Our findings demonstrate cognitive decline in a subset of MG patients, as evidenced by lower neuropsychological scores. The association between these deficits and quantitative EEG measures supports the existence of a functional neurophysiological correlate. qEEG may therefore represent a valid, easily applicable tool to complement cognitive scales in quantifying impairment within this population.

MYASTHENIA

Abstract P081 - Cod. 143505

COMPLEMENT PROTEIN MODULATION AND PHARMACODYNAMIC BIOMARKERS DURING Eculizumab- AND Ravulizumab-Mediated C5 Inhibition in Generalized Myasthenia Gravis

Bonanno S.*, Frangiamore R., Iacomino N., Vanoli F., Tarasco

M.C., Berni A., Rinaldi E., Canella M., Salerno F., Giacopuzzi Grigoli E., Cheli M., Andreetta F., Mantegazza R., Maggi L., Antozzi C., Cavalcante P.
Neurology 4 - Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, Milano, Italy

The complement cascade is a key pathogenic effector in anti-acetylcholine receptor (AChR) antibody-positive myasthenia gravis (MG) and represents both a therapeutic target and a source of potential pharmacodynamic biomarkers. Eculizumab (ECU) and ravulizumab (RAVU) are C5-targeting complement inhibitors approved for treatment of generalized MG (gMG). While clinical efficacy and functional complement inhibition are well established, longitudinal effects on circulating complement proteins in real-world clinical settings are still poorly defined.

We conducted a prospective, exploratory study to characterize plasma complement protein dynamics in AChR-gMG patients treated with ECU or RAVU.

Twenty-two patients (ECU n = 11; RAVU n = 11) were followed for six months. Plasma complement proteins were measured longitudinally by multiplex immunoassays and ELISA, clinical outcomes (MG-ADL, QMG, and MGC scores) were collected accordingly.

Both C5 inhibitors induced rapid and sustained modulation in selected circulating complement proteins, together with significant clinical improvement over the treatment period. Plasma C5 levels significantly increased from baseline as early as week 2 and remained elevated throughout follow-up in ECU- (p < 0.01) and RAVU- (p < 0.005) treated patients, consistent with reduced C5 consumption under functional C5 blockade and possible compensatory synthesis. In ECU-treated patients, C9 was also significantly increased (p < 0.05) while C4b was reduced (p < 0.05) at early time points (week 2-3), with comparable early trends observed in RAVU-treated patients, reflecting effective inhibition of terminal complement activation.

Our results identify a circulating complement protein signature associated with C5 inhibition and support the potential of complement components as pharmacodynamic biomarkers for monitoring complement-targeted therapies in MG, warranting further validation in larger cohorts.

MYASTHENIA

Abstract P083 - Cod. 143485

CONGENITAL MYASTHENIC SYNDROMES: CLINICAL AND GENETIC SPECTRUM FROM A SINGLE ITALIAN REFERRAL CENTER

Luppino F.*, Pugliese A., Biasini F., Natoli S., Terranova C., Rizzo V., Toscano A., Rodolico C.
Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

Congenital myasthenic syndromes (CMS) are a heterogeneous group of genetic disorders affecting the neuromuscular transmission, as a result of mutations in proteins essential for the organization, maintenance, functioning, or regulation of the neuromuscular junction. We report the clinical, genetic, and therapeutic features of a cohort of

CMS patients followed for a mean time of 15.3 years (SD 14.3; range 1 – 56) at our centre

Clinical records of 22 genetically confirmed CMS patients have been retrospectively reviewed. The most recurrent gene was CHRNE (n = 13), followed by GFPT1 (n = 3), while CHRNA1, CHRND, GFPT2, DOK7, SLC5A7 and CHAT mutations were each identified in one patient. Age at symptom onset ranged from infancy to adulthood.

Ocular involvement was the most frequent presentation at the disease onset. Bulbar muscles weakness was observed in 5 patients (23%), while neonatal or early hypotonia was reported in 2 patients (9%). Furthermore, dysmorphic features were identified in half of patients.

Along the course of the disease, 73% of patients variably developed axial involvement and 68% proximal limb muscles weakness. A predominantly distal pattern was rare, being observed only in one patient. Isolated ocular involvement with no clear axial or limb muscles weakness was documented in 4 patients.

Finally, respiratory involvement was reported in only three patients: one of them required oxygen therapy, while the other two ventilatory support.

All the patients were treated with acetylcholinesterase inhibitors, except for the DOK7-mutated patient who was treated with 3,4-diaminopyridine. In addition with pyridostigmine, four patients were treated with 3,4-diaminopyridine (CHRNE-mutated), two patients with ephedrine (one CHRNE-mutated and one GFT-1-mutated), one patient with fluoxetine (GFPT-1-mutated), and another one with salbutamol (SLC5A7-mutated).

In our cohort of patients, CHRNE is the most frequently involved gene. Ocular symptoms were the most common initial manifestations, while axial and proximal limb muscles involvement frequently developed along the disease course

MYASTHENIA

Abstract P085 - Cod. 143330

CORRELATION BETWEEN CLINICAL RESPONSE AND MUSK-AB CHANGES IN PATIENTS TREATED WITH ROZANOLIXIZUMAB

Falso S.², Vanoli F.¹, Rini N.³, D'Alvano G.⁴, Valenzano G.², Frangiamore R.¹, Marini S.², Brighina F.³, Habetzwallner F.², Rigamonti A.⁵, Biseco A.⁴, Di Stefano V.³, Maggi L.¹, Iorio R.²

¹ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ² Department of Neuroscience, Catholic University of the Sacred Heart, Roma, Italy, ³ Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), Palermo, Italy, ⁴ Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Napoli, Italy, ⁵ Department of Neurosciences ASST Lecco, Neurology Unit, A. Manzoni Hospital, Lecco, Italy

Rozanolixizumab, a monoclonal antibody targeting neonatal Fc receptor, has been approved for patients with muscle-specific kinase antibody positive myasthenia gravis (MuSK-MG). MuSK-Abs belong to the IgG4 subclass and are thought to correlate with disease severity. However, real-world data on rozanolixizumab efficacy in MuSK-

MG are lacking. This multicenter study aimed to assess the clinical response to rozanolixizumab in a cohort of MuSK-MG patients and to investigate changes of MuSK-Ab titers using live cell-based assay (L-CBA).

We enrolled MuSK-MG patients treated with rozanolixizumab. Baseline characteristics, clinical efficacy, and biological data were collected. Myasthenia Gravis-Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales were used to assess clinical efficacy. Steroid dose changes were also evaluated. MuSK-Ab titers were measured at baseline and at the end of treatment cycle using L-CBA.

Thirty-eight MuSK-MG patients were included. Median age at MuSK-MG onset was 38.5 (range 13-68). Two patients did not complete the first treatment cycle. Both MG-ADL and QMG score significantly improved from baseline ($p < 0.0001$ and $p = 0.0004$, respectively), while daily steroid dose was not significantly reduced. Fourteen (38.9%) patients achieved minimal symptom expression (MSE) at the end of cycle. MuSK-Ab titers were tested in nine patients and demonstrated a significant reduction from baseline ($p = 0.008$).

Our findings show that rozanolixizumab is an effective add-on treatment in MuSK-MG, leading to significant reductions in MG-related disability. Further investigations will clarify whether reductions in antibody titers translate to sustained clinical improvements.

MYASTHENIA

Abstract P087 - Cod. 142943

CORRELATION BETWEEN IGG REDUCTION AND CLINICAL IMPROVEMENT IN MYASTHENIA GRAVIS PATIENTS TREATED WITH EFGARTIGIMOD ALFA

Meli A.^{*}, Magri M., Campo S., Di Martino G., D'Amico F., Rini N., Labate A., Brighina F., Di Stefano V.

Biomedicine, Neuroscience and Advanced Diagnostic (Bi.N.D.) Department, University of Palermo, Palermo, Italy

Myasthenia Gravis (MG) is an autoimmune disorder caused by IgG autoantibodies targeting AChR, MuSK or LRP4, impairing neuromuscular transmission. Efgartigimod alfa, a human IgG1 antibody fragment, binds the neonatal Fc receptor (FcRn) to selectively reduce circulating IgG, including pathogenic autoantibodies, without affecting other immunoglobulins.

This study investigated whether reductions in IgG following efgartigimod alfa treatment correlate with clinical improvement measured by MG-ADL and QMG scores. Twenty MG patients treated with efgartigimod alfa (iv o sc) at the Center for Rare Diseases of the A.O.U.P. of Palermo were enrolled. Serum IgG levels, MG-ADL and QMG scores were assessed before and after treatment. Pre-post differences were analyzed using paired t-tests or Wilcoxon signed-rank tests according to data distribution. Changes from baseline (Δ values) were calculated. Associations between Δ IgG and clinical changes were assessed using Spearman's rank correlation. Exploratory threshold analyses were conducted using independent-sample tests (independent t-test or Mann-Whitney U test).

Efgartigimod alfa induced a significant reduction in total IgG levels

($p < 0.001$) and significant improvements in MG-ADL and QMG scores (both $p < 0.01$). No significant correlation was observed between the magnitude of IgG reduction and clinical improvement. Threshold-based analyses similarly failed to demonstrate a relationship between IgG depletion and clinical response.

Efgartigimod alfa effectively reduces IgG levels and improves clinical outcomes in MG. However, the lack of a dose–response relationship between IgG reduction and clinical improvement indicates that total IgG depletion alone does not fully explain clinical response to FcRn inhibition.

MYASTHENIA

Abstract P089 - Cod. 143070

CORTICOSTEROID DOSE TAPERING DURING TREATMENT WITH ROZANOLIXIZUMAB IN PATIENTS WITH GENERALISED MYASTHENIA GRAVIS: POST HOC ANALYSIS

Bonanno S.^{*1}, Antozzi C.², Habib A.³, Pascuzzi R.⁴, Sacconi S.⁵, Utsugisawa K.⁶, Vu T.⁷, Grimson F.⁸, Snipes R.⁹, Tarancón T.¹⁰, Brill V.¹¹

¹ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS, Istituto Neurologico Carlo Besta, Milan, Italy, ² Immunotherapy and Apheresis Unit and Neuroimmunology and Muscle Pathology Unit, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Neurologico Carlo Besta, Milan, Italy, ³ MDA ALS & Neuromuscular Center, Department of Neurology, University of California, Irvine, Orange, United States of America, ⁴ Neurology Department, Indiana University School of Medicine, Indiana University Health, Indianapolis, United States of America, ⁵ Université Côte d'Azur, Peripheral Nervous System & Muscle Department, Pasteur 2 Hospital, Centre Hospitalier Universitaire de Nice, Nice, France, ⁶ Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, ⁷ Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, United States of America, ⁸ UCB, Slough, United Kingdom, ⁹ UCB, Morrisville, United States of America, ¹⁰ UCB, Madrid, Spain, ¹¹ Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Toronto General Hospital, University of Toronto, Toronto, Canada

Long-term efficacy and safety of rozanolixizumab were assessed in adults with generalised myasthenia gravis in the double-blind, Phase 3, MycarinG study (NCT03971422) and its open-label extensions (OLEs), MG0004 (NCT04124965) and MG0007 (NCT04650854). Concomitant corticosteroids were permitted during the studies, although reducing corticosteroid use is often desirable due to potential side effects and long-term toxicities.

In MycarinG, rozanolixizumab was administered once weekly in a 6-week cycle. Following an initial cycle in MG0007, subsequent administration was symptom-driven. The objective of this post hoc analysis was to assess the proportion of patients who had their OLE corticosteroid dose reduced, discontinued or increased relative to double-blind baseline. Investigators could start a new cycle of rozanolixizumab, or reduce, increase, start or stop corticosteroids at their own discretion. Final data were pooled across MycarinG and MG0007.

Overall, 121 patients were included, of whom 66.1% ($n = 80/121$) had no change in corticosteroid dose (mean 7.49 [range 0.0–80.0]

mg/day), and 13.2% ($n = 16/121$) had their corticosteroid dose increased, which included 5.8% ($n = 7/121$) who started corticosteroids. Of patients receiving corticosteroids at baseline ($n = 67/121$), 37.3% ($n = 25/67$) decreased their corticosteroid dose, including 17.9% ($n = 12/67$) who discontinued corticosteroids. Of patients receiving corticosteroids ≥ 7.5 mg/day (Cushing threshold) at baseline ($n = 53/121$), 41.5% ($n = 22/53$) decreased their corticosteroid dose, including 18.9% ($n = 10/53$) who discontinued corticosteroids. Over a third of study patients were able to decrease or discontinue corticosteroids while receiving long-term cyclic rozanolixizumab treatment, without protocol guidance on corticosteroid tapering. Funding: UCB.

MYASTHENIA

Abstract P091 - Cod. 143280

DESIGN OF A PHASE 4, OPEN-LABEL, SINGLE-GROUP STUDY TO EVALUATE CLINICAL OUTCOMES OF EFGARTIGIMOD PH20 SC IN ADULT PARTICIPANTS WITH NEW-ONSET GENERALIZED MYASTHENIA GRAVIS

De Notariis A.^{*1}, Habib A.A.², Govindarajan R.³, Li L.¹, Giacobbe J.¹, Guptill J.T.¹

¹ argenx, Ghent, Belgium, ² Department of Neurology, University of California, Irvine, Orange, United States of America, ³ HSHS St. Elizabeth's Hospital, O'Fallon, United States of America

Efgartigimod, a human immunoglobulin G1 antibody Fc fragment that blocks neonatal Fc receptor, has been investigated in several Phase 3 generalized myasthenia gravis (gMG) studies. Analyses from previous studies suggest efgartigimod treatment early in the disease course led to improvements in participants with acetylcholine receptor antibody–positive (AChR-Ab+) gMG. Emerging literature suggests initiating therapy early after disease onset may maximize outcomes in patients with gMG. Here, we provide the design of a Phase 4, open-label, single-group trial that assesses clinical outcomes of administration of subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) in participants with new-onset generalized myasthenia gravis (gMG).

ADAPT-EARLY will enroll ~30 adults with AChR-Ab+ gMG (Myasthenia Gravis Foundation of America Class II-IV) whose onset of gMG signs/symptoms occurred ≤ 12 months before screening (participants with onset of ocular MG signs/symptoms ≤ 24 months before screening may be enrolled) and are either gMG treatment-naïve or have only received treatment with acetylcholinesterase inhibitors. Participants will receive 4 once-weekly injections followed by every-other-week dosing of efgartigimod PH20 SC 1000 mg (via a prefilled syringe) for a total treatment period of 51 weeks followed by a 4-week safety follow-up period.

The primary endpoint is proportion of participants who achieve minimal symptom expression (MG-ADL of 0–1) at any time within the first 16 weeks of efgartigimod PH20 SC treatment. Additional efficacy/steroid-sparing, safety/tolerability, and pharmacokinetic/pharmacodynamic outcomes are also being assessed.

Results of this Phase 4 trial will provide valuable efgartigimod PH20

SC clinical outcome and safety data for the treatment of new-onset gMG.

MYASTHENIA

Abstract P093 - Cod. 142685

DO WE REALLY NEED NON-STEROIDAL IMMUNOSUPPRESSANTS IN GENERALIZED MYASTHENIA GRAVIS TREATED WITH NEW TARGETED THERAPIES? A PILOT STUDY

Vera V.^{*1}, Rossini E.¹, Morino S.², Antonini G.¹, Leonardi L.², Garibaldi M.¹, Lauletta A.¹, Forcina F.¹, Tufano L.¹, Marando D.¹, Fionda L.²

¹ Department of Neuroscience, Mental Health and Sensory Organs (NEMOS), SAPIENZA University of Rome, Rome, Italy, ² Neuromuscular and Rare Diseases Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy

Targeted biologic therapies, including complement and neonatal Fc receptor (FcRn) inhibitors, have transformed the treatment of generalized myasthenia gravis (gMG). However, the role of concomitant non-steroidal immunosuppressants (NSIST) remains uncertain. This study evaluated whether background NSIST influences clinical outcomes and corticosteroid reduction in gMG patients treated with targeted therapies.

Twenty patients received background NSIST (Group 1), while 21 did not (Group 2). Baseline MG-ADL scores and corticosteroid doses were comparable between groups (9.10 ± 4.36 vs 8.24 ± 3.38) (22.17 ± 13.81 mg vs 22.06 ± 16.43). Baseline QMG scores were slightly higher in Group 1 (14.0 ± 5.1 vs 10.9 ± 4.8 ; $p = 0.049$). Both groups showed significant improvement in MG-ADL and QMG scores at all follow-up time points, without differences in clinical scale improvement comparing the two groups. Rates of MSE achievement, MGFA-PIS improvement, and corticosteroid tapering did not differ between groups. Our pilot analysis indicates that concomitant use of NSIST does not appear to be associated with greater improvement in clinical outcomes, enhance corticosteroid-sparing effects or increased disease stability. Larger, prospective studies are needed to optimize treatment strategies in gMG.

MYASTHENIA

Abstract P095 - Cod. 143059

EARLY AND SUSTAINED RESPONSE OVER TIME WITH ZILUCOPLAN IN GENERALISED MYASTHENIA GRAVIS: 120-WEEK POST HOC ANALYSIS OF RAISE-XT

Cheli M.^{*1}, Bresch S.², Freimer M.³, Hewamadduma C.⁴, Leite M.I.⁵, Maniaol A.⁶, Utsugisawa K.⁷, Beau Lejdstrom R.⁸, Boroojerdi B.⁹, Grimson F.¹⁰, Savic N.⁸, Howard J.¹¹

¹ Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Nazionale Neurologico Carlo Besta, Milan, Italy, ² Service de Neurologie, Hospital Pasteur, Centre Hospitalier Universitaire de Nice, Nice, France, ³ Department of Neurology, The Ohio

State University Wexner Medical Center, Columbus, OH, United States of America, ⁴ Academic Neuroscience Unit, Sheffield Teaching Hospitals NHS Foundation Trust; Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, United Kingdom, ⁵ Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom, ⁶ Department of Neurology, Oslo University Hospital, Oslo, Norway, ⁷ Department of Neurology, Hanamaki General Hospital, Hanamaki, Hanamaki, Japan, ⁸ UCB, Bulle, Switzerland, ⁹ UCB, Monheim, Germany, ¹⁰ UCB, Slough, United Kingdom, ¹¹ Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States of America

RAISE-XT (NCT04225871), an ongoing, Phase 3, open-label extension study in patients with anti-acetylcholine receptor antibody-positive generalised myasthenia gravis (MG), showed clinically meaningful and sustained improvements in MG-specific outcomes with zilucoplan, a complement component 5 inhibitor.

In RAISE-XT, adults who completed a qualifying double-blind study (NCT03315130/NCT04115293) self-administered once-daily subcutaneous zilucoplan 0.3mg/kg. This post hoc analysis assessed durability of response to Week 120 of zilucoplan treatment in early (double-blind Week 1) MG Activities of Daily Living (MG-ADL) and Quantitative MG (QMG) responders. Response was defined as ≥ 3 -point (MG-ADL) and ≥ 5 -point (QMG) improvement from double-blind baseline without rescue therapy. The percentage of time spent in response was calculated (interim data cut: 11 November 2023). Overall, 93 patients received zilucoplan 0.3mg/kg in the double-blind studies; 43.0% ($n = 40/93$) were MG-ADL responders and 33.3% ($n = 31/93$) were QMG responders at Week 1. Week 1 MG-ADL and QMG responders spent a median (range) of 98.9% (5.8–99.2) and 99.0% (2.5–99.2) of their time in response up to Week 120, respectively. Week 1 MG-ADL and QMG non-responders spent a median (range) of 84.6% (0.0–98.3) and 66.7% (0.0–98.9) of their time in response up to Week 120, respectively, with most responding later in the study.

Among early responders, time in response remained high (99%) up to Week 120. Among Week 1 non-responders, over two-thirds of time was spent in response through to Week 120, showing that most patients became responders with continued zilucoplan use. These data demonstrate rapid and sustained efficacy with long-term zilucoplan treatment. Funding: UCB.

MYASTHENIA

Abstract P097 - Cod. 142865

EVALUATING THE IMPACT OF SWITCHING COMPLEMENT INHIBITORS: RAVULIZUMAB AFTER ECUZUMAB IN ACHR+ GENERALIZED MYASTHENIA GRAVIS PATIENTS

Capuozzo F.^{*}, D'Alvano G., D'Anna F., Marigliano D., Sansone R., Todisco V., Tessitore A., Bisecco A.

Department of Advanced Medical and Surgical Sciences – University of Campania “Luigi Vanvitelli, Napoli, Italy

Complement system plays a key role in the pathogenesis of Myasthenia Gravis (MG). Eculizumab and Ravulizumab are humanized monoclonal antibodies (mAbs) targeting C5 complement protein, approved

for treatment of refractory generalized MG (gMG) associated with anti-acetylcholine receptor antibodies (AChR+). Ravulizumab has a longer half-life, allowing less frequent dosing.

Our aim was to assess safety, efficacy, and tolerability of switching from Eculizumab to Ravulizumab in a cohort of patients with AChR+ gMG.

All AChR+ gMG patients who switched from Eculizumab to Ravulizumab followed at our department were included. Outcome measures were MG-Activities of Daily Living (MG-ADL), MG Quality of Life-15 (MGQoL-15), Neuro-QoL short form (sf), and Treatment Satisfaction Questionnaire for Medication (TSQM-9). Data were collected at baseline (T0), after 2 (T1), 4 (T2) and 6 weeks (T3) and then at each infusion.

Data from 6 adult patients were analyzed. Neuro-QoL sf decreased significantly between T0 and T2, remaining stable afterwards. MGQoL-15 and TSQM-9 scores did not change significantly. However, TSQM-9 revealed patient preference for Eculizumab in effectiveness, whereas global satisfaction favored Ravulizumab. MG-ADL scores decreased from 2.5 (T0) to 1.5 (T1) and then remained stable. No adverse drug reactions occurred.

Our results suggests that patients were satisfied with both Eculizumab and Ravulizumab. Switching to Ravulizumab did not impact quality of life, despite the need for hospital-based infusions. Ravulizumab was generally preferred, mainly due to greater treatment planning flexibility. Therapeutic benefits were maintained. Longer-term studies are warranted to better characterize the long-term efficacy and patient-reported outcomes of Ravulizumab in gMG.

MYASTHENIA

Abstract P099 - Cod. 143347

EYELID MYOTONIA-LIKE PHENOMENON IN A PATIENT AFFECTED BY MYASTHENIA GRAVIS AND GRAVES' ORBITOPATHY

Cortese F*, Brienza M., De Giglio L., Pennisi E.M.

Rare and Neuromuscular Diseases Center, Unit of Neurology, San Filippo Neri Hospital, Rome, Italy

Few patients affected by Myasthenia gravis (MG) and concomitant eyelid myotonia-like phenomenon have been described so far (Abraham, 2023). All of them were male patients with late-onset MG with anti-AChR antibodies.

We report the case of a MG patient exhibiting eyelid-myotonic phenomenon, during treatment with pyridostigmine.

The patient is a 75 years' old man who, after Covid-19 infection, developed a rapidly worsening diplopia. Neurological examination showed a complex and fluctuating oculomotor dysfunction (bilateral impaired adduction and elevation), exophthalmos and mild bilateral ptosis.

Both TSH receptor antibodies and acetylcholine receptor antibodies were found in his blood.

Single fibre EMG was positive for a dysfunction of the neuromuscular transmission. A double diagnosis of Basedow disease and Myasthenia gravis was made.

He started a therapy with methimazole, pyridostigmine and steroids with clinical benefit. In the following months the therapy was gradually tapered.

After about three years from the beginning of the therapy, he started to report a relevant difficulty in opening his eyes after a forced closure. This symptom tended to reduce after exercise.

Needle examination found myotonic discharges in the facial muscles. After reducing and then interrupting the therapy with pyridostigmine, these symptoms disappeared.

While in the previously reported patients the symptom started at the beginning of the disease, in our patient the problem started years later and disappeared after pyridostigmine discontinuation. Therefore, in our case, probably, the excess of acetylcholine induced by pyridostigmine in a dysfunctional neuromuscular junction was able to induce a prolonged contraction of the orbicularis oculi muscles.

MYASTHENIA

Abstract P101 - Cod. 143429

FALSE-POSITIVE MYASTHENIA GRAVIS ANTIBODIES: DIAGNOSTIC PITFALLS AND CLINICAL CONSEQUENCES

Giannoccaro M.P.*¹, Ballestracci C.², Serra L.³, De Pasqua S.¹, Di Stasi V.¹, Vacchiano V.¹, Fetta A.⁴, Rossi S.⁵, Ricciardiello F.³, Gligora I.², Morelli L.³, Cordelli D.M.⁴, Donadio V.³, Liguori R.¹

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy, ² Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ³ IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Patologia Neuromuscolare e Neuroimmunologia, Bologna, Italy, ⁴ IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età Pediatrica, Bologna, Italy, ⁵ IRCCS Istituto Delle Scienze Neurologiche Di Bologna, UOC Clinica Neurologica - Rete Neurologica Metropolitana (NEUROMET), Bologna, Italy

Autoantibody testing is central to myasthenia gravis (MG) diagnosis, but increasing accessibility raises concern for false-positive results and clinical impact.

We aimed to characterize testing contexts, identify factors associated with false positivity, and assess downstream clinical consequences. We retrospectively reviewed patients referred for second-opinion AChR/MuSK testing after prior positive results (January 2020-November 2025). Clinical data, investigations, treatments, and outcomes were collected. Pre-test probability was independently rated by two neurologists. All positive samples were reassessed using live and/or fixed cell-based assays (CBA).

Of 83 patients with prior positive serology, only 9 (10.8%) were confirmed antibody-positive by CBA (8 AChR, 1 MuSK) and diagnosed with MG; 74 (89.2%) represented false-positive results. Confirmed MG cases generally had intermediate-to-high pre-test probability and were referred mainly to confirm diagnosis because of atypical features/comorbidities. In contrast, false-positive cases predominantly had low pre-test probability (64.9%) and were referred primarily to exclude MG (75.7%). False-positive results prompted extensive investigations, including neurophysiology (79.7%) and chest imaging (55.4%), with a median of three neurological consultations. Seventeen patients (23%) received pyridostigmine and 10 (13.5%) were provisionally diagnosed with MG, some receiving immunosuppressive therapy. Diagnostic delay was significantly longer in patients ini-

tially labeled as MG (median 58 vs 5.5 months, $p < 0.0001$). False-positive cases frequently showed concomitant autoimmune diseases or additional autoantibody positivity, suggesting that immune dysregulation may contribute to nonspecific ELISA reactivity. False-positive MG antibody results are associated with diagnostic delay, unnecessary investigations, and inappropriate treatments. Careful clinical preselection and confirmatory testing are essential to minimize harm and optimize diagnostic accuracy.

MYASTHENIA

Abstract P059 - Cod. 143514

AGE-ADJUSTED PERIPHERAL IMMUNE PROFILING REVEALS DISTINCT T-CELL SIGNATURES IN JUVENILE MYASTHENIA GRAVIS

Fetta A.^{*1}, Corsini C.¹, Moratti M.², Baldini L.², Di Pisa V.¹, Conti F.², Cordelli D.M.¹

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età Pediatrica, Bologna, Italy; ² Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy, Bologna, Italy, ² Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Bologna, Italy ³ Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, Bologna, Italy

Juvenile myasthenia gravis (JMG) is a rare antibody-mediated disorder affecting the neuromuscular junction. While effector mechanisms are well characterized, the cellular immune drivers remain incompletely understood. In pediatric patients, physiological age-related immune maturation complicates direct comparisons with adult data, and age-adjusted studies on immune profiling are currently lacking. Prospective observational study including patients with JMG aged 1–18 years, with any prior immunosuppressive therapies discontinued for at least 6 months. Clinical phenotype, serology, and extended peripheral blood immunophenotyping were assessed. Immune subsets were analyzed using age-adjusted percentile ranges from literature. Group comparisons were performed using the Mann–Whitney U test ($P < 0.05$).

Ten patients included (5 females/5 males; median age 12.97 IQR 7.05–13.61); 8 had generalized MG and 2 ocular MG. Median time from onset was 550 days (IQR 60–1245). CD3⁺ T-cell values were within the age-adjusted normal range in all patients. CD4⁺ T-cell values above the 95th percentile were observed in a single generalized AChR-positive patient, while CD4⁺ effector memory T cells exceeded the 95th percentile in five patients. Regulatory T cells were below the 5th percentile in two patients, although min–max scores clustered around zero across the cohort. In contrast, the potentially regulatory TCR $\gamma\delta$ ⁺ T-cell absolute values were below the 5th percentile in five patients, all with generalized MG.

JMG displays age- and phenotype-associated immune signatures that are partially distinct from adult MG. Age-adjusted immune profiling enables age-tailored characterization within pediatric cohorts. Elevated CD4⁺ effector memory and reduced $\gamma\delta$ and T cells characterize generalized disease, whereas ocular MG shows relative preservation of these compartments. These findings support further

age-stratified studies to identify pediatric-specific immunological biomarkers of disease and treatment response.

MYASTHENIA

Abstract P103 - Cod. 143285

FATIGUE PREDICTS PATIENT SATISFACTION IN MYASTHENIA GRAVIS: INSIGHTS FROM THE MYREALWORLD MG STUDY

Salvucci G.^{*}, Bonanno S., Cheli M., Giacomuzzi E., Vanoli F., Frangiamore R., Mantegazza R., Antozzi C., Maggi L. *Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta., Milano, Italy*

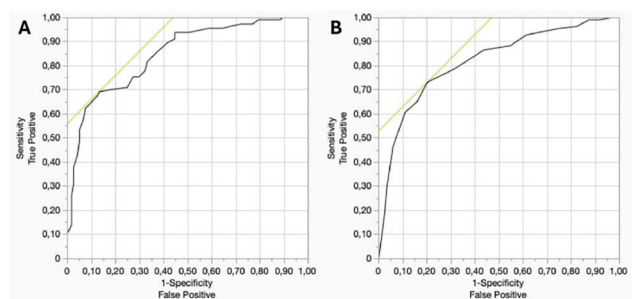
Treatment goals in myasthenia gravis (MG) are increasingly focusing on patient-reported outcomes (PROMs). The Patient Acceptable Symptom State (PASS) reflects overall patient satisfaction with their current condition.

To evaluate whether fatigue, measured by FACIT-Fatigue, predicts PASS independently of daily activities performance (MG-Activities of Daily Living, MG-ADL) in MG.

We analyzed data from MyRealWorld MG, an international application sponsored by Vitaccess, matching FACIT-Fatigue scores and other PROMs, including MG-ADL and Hospital Anxiety and Depression Scale (HADS), with PASS response through ROC curves analysis.

Among 231 observations from 199 patients (mean age 50.9 ± 13.6 , $F = 140$, 70%), mean FACIT-Fatigue score was 29.6 ± 11.6 ; PASS was achieved in 112 observations (48%). FACIT-Fatigue showed higher discriminative ability for PASS responses (AUC 0.849, figure A) than MG-ADL (AUC 0.819, figure B); HADS-anxiety/depression did not predict PASS (AUC ~ 0.60). In a multivariable logistic regression analysis, FACIT-Fatigue remained significantly associated with PASS (OR 1.16, 95% CI 1.11–1.20, $p < 0.001$) after adjusting for MG-ADL. Interestingly, a cut-off of FACIT > 30 , as already established in literature, was a better predictor of satisfaction according to PASS than $MG-ADL \leq 2$ (SE 0.75 vs 0.47, $p < 0.001$). Additionally, when considering $MG-ADL \leq 2$ ($n = 59$, 25%), FACIT-Fatigue score was significantly lower in PASS-negative ($n = 9$, 15%) than PASS-positive ($n = 50$, 85%) individuals ($p = 0.0036$).

Fatigue plays an important role in determining MG patient satisfaction according to PASS, regardless of functional impairment and anxiety/depression comorbidities. Our results highlight the importance of



fatigue evaluation in MG patients to detect unmet needs unnoticed by traditional assessments.

MYASTHENIA

Abstract P105 - Cod. 142951

FIBRINOGEN SERUM LEVEL AS BIOMARKER OF DISEASE ACTIVITY IN MYASTHENIA GRAVIS

Di Martino G.^{*}, D'Amico F., Rini N., Meli A., Mineo M., Brighina F., Di Stefano V.

Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo., Palermo, Italy

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction at the postsynaptic membrane. One study found significantly elevated fibrinogen levels in the serum of patients with MG; however, a subsequent analysis did not reveal this association.

The aim of our study is to investigate the possible correlation between serum fibrinogen levels and clinical disease activity in patients with MG. Fibrinogen levels were detected using the Clauss method on the serum of patients admitted to DH, DS or ordinary regimen. Each enrolled patient was administered clinical assessment scales such as Myasthenia Gravis Activity of Daily Living (MG-ADL), Myasthenia Gravis Composite (MGC), and Myasthenia Gravis Quantitative (QMG) scales.

In the 70 enrolled patients, the mean fibrinogen value detected was 332 ± 78.7 mg/dl; mean MG-ADL 10 ± 4 ; mean QMG 16 ± 6 ; mean

MGC 13 ± 6 . The Spearman's correlation test did not highlight any statistically significant correlation between serum fibrinogen levels and clinical assessment scale scores in patients with MG, although the scatterplot shows a weak positive trend.

Although fibrinogen is recognized as an immunoinflammatory mediator involved in several autoimmune disease, our real-life data don't show a correlation with the clinical scales used to evaluate MG patients; therefore, fibrinogen is not a reliable biomarker of disease activity. Further studies are needed to identify serum markers that more accurately reflect disease activity.

MYASTHENIA

Abstract P107 - Cod. 142984

FIRST-MONTH CLINICAL RESPONSE TO C5 COMPLEMENT INHIBITION AND FCN ANTAGONISTS IN GENERALIZED MYASTHENIA GRAVIS

Rini N.^{*1}, Messina C.², Lima S.M.¹, Lo Mauro E.¹, Brighina F.¹, Di Stefano V.¹

¹ Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy, ² Azienda Sanitaria Provinciale Catania, Catania, Italy

Generalized myasthenia gravis (gMG) is a heterogeneous autoimmune disorder in which rapid symptom control is often required. Complement C5 inhibitors (C5IT) and neonatal Fc receptor (FcRn)

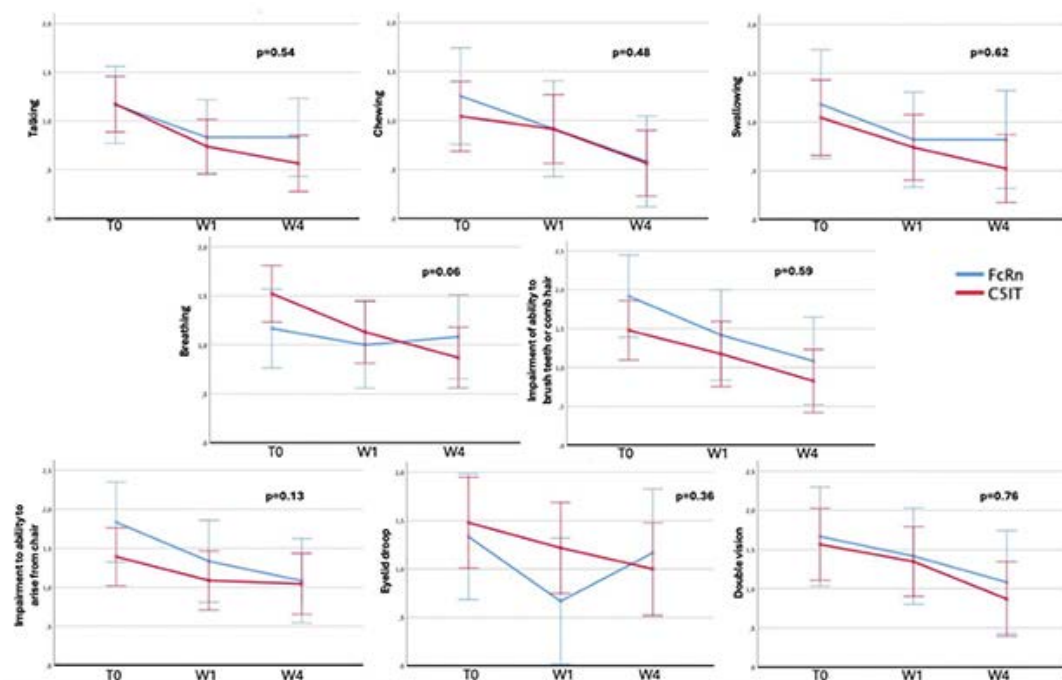


Figure 2. MG-ADL subitems comparison with C5IT and FcRn at baseline, and after 1 and 4 weeks of treatment. MG-ADL, Myasthenia Gravis Activities of Daily Living scale. T0, baseline; W1, after 1 week of treatment; W4, after 4 weeks of treatment.

antagonists have recently expanded therapeutic options for refractory gMG, but comparative real-world data on their very early clinical effects are scarce.

This study aimed to evaluate the short-term efficacy and safety of C5IT and FcRn antagonists in gMG and compare these different approaches identifying possible predictive factors to help the clinician in the therapeutic choice.

In this observational real-life study, we enrolled Thirty-seven patients (25 females, 68%) with gMG who received only C5IT and FcRn. C5IT consisted of 24 patients (65%), whereas FcRn of 13 patients (35%). A significant reduction was observed in MG-ADL ($\Delta = -4.3 \pm 3.3$; $p < 0.05$) and QMG ($\Delta = -6.9 \pm 7.4$; $p < 0.05$) scores at week 4. MG-ADL responders increased from 41% at week 1 to 68% at week 4, while QMG responders rose from 16% to 46%. Minimal symptom expression was achieved in 8.1% of patients at week 4. Subitem analysis revealed improvement in all MG-ADL domains except ptosis. Logistic regression identified diplopia as an independent predictor of non-response.

Patients obtained a consistent clinical response from the first week, achieving a good stability of MG-ADL and QMG scores. Ocular involvement might be a predictor of non-response in the short term. This study confirms the overall efficacy of both C5IT and FcRn antagonists, supporting their role as effective treatment options in patients with gMG.

MYASTHENIA

Abstract P109 - Cod. 143476

IMMUNO-MEDIATED MUSCLE HYPEREXCITABILITY: TWO CASES OF RIPPLING MUSCLE DISEASE, ONE ASSOCIATED WITH MYASTHENIA GRAVIS

Fornasier T.², Pauro A.², Petrosino A.², Capece G.², Sogus E.², Dubey D.¹, Milone M.¹, Sorarù G.², Bello L.², Minicuci G.M.³, Pegoraro E.²

¹ Department of Neurology, Mayo Clinic College of Medicine, Rochester, United States of America, ² Department of Neurosciences, University of Padova, Padova, Italy, ³ Clinica Neurologica, Padova University Hospital, Padova, Italy

Rippling muscle disease (RMD) is a rare disorder of muscle hyperexcitability characterized by wave-like muscle contractions triggered by mechanical stimulation or voluntary contraction. Two forms are recognized: hereditary RMD (hRMD), associated with pathogenic variants in CAV3 or CAVIN1/PTRF, and immune-mediated RMD (iRMD), which is could be associated with autoimmune conditions, most notably myasthenia gravis (MG). Anti-cavin-4 antibodies serve as a specific serological biomarker for iRMD, while mosaic expression of caveolin-3 and cavin-4 on muscle biopsy represents its histopathological hallmark.

We report two cases of iRMD, one of which associated with MG.

The first patient was a 66-year-old man with celiac disease and diabetes who presented with cramp-like sensations and diffuse spontaneous muscle movements. Over time, he developed dysphagia,

dysarthria, and proximal muscle fatigability, leading to a diagnosis of MG. Laboratory findings revealed mildly elevated creatine kinase (CK) levels and positivity for anti-acetylcholine receptor and anti-titin antibodies. Clinical evidence of muscle rippling raised suspicion of iRMD, which was confirmed by strong anti-cavin-4 IgG positivity. Thymectomy showed an involuted thymus focal hyperplasia. The second patient was a 33-year-old woman who developed diffuse myalgia and rippling muscle movements after her second delivery, with a relapsing-remitting course. CK were intermittently elevated, thymic hyperplasia was detected on MRI, and muscle biopsy revealed mild myopathic changes with partial caveolin-3 deficiency. Genetic testing and autoimmune serology were negative.

These cases emphasize the importance of recognizing iRMD in patients with neuromuscular symptoms, particularly when associated with MG, as this may have relevant therapeutic implications.

MYASTHENIA

Abstract P111 - Cod. 143287

IMPACT OF EFGARTIGIMOD TREATMENT ON OVERALL DISEASE EXPERIENCE IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS: DESIGN OF THE POEMA STUDY

Bisecco A.^{*1}, Rossi S.², De Notariis A.², Barelo S.³, Signori A.⁵, Clerico M.⁶, Iorio R.⁴, Sufragiu D.⁷, Mantegazza R.⁷

¹ Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Naples, Italy, ² argenx Italy Srl, Milan, Italy, ³ Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy, ⁴ Department of Neuroscience, Università Cattolica del Sacro Cuore; Neurology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ⁵ Department of Health Sciences, University of Genoa; IRCCS Ospedale Policlinico San Martino, Genoa, Italy, ⁶ Department of Clinical and Biological Sciences, University of Turin; San Luigi Gonzaga University Hospital, Turin, Italy, ⁷ Associazione Italiana Miastenia e Malattie Immunodegenerative, Milan, Italy

Efgartigimod is a human immunoglobulin G1 (IgG1) antibody Fc fragment that blocks the neonatal Fc receptor. Phase 3 trials and real-world evidence demonstrated that efgartigimod is efficacious and well tolerated in patients with generalized myasthenia gravis (gMG), but there remains a need to understand the impact of efgartigimod in wider real-world clinical settings. We present the design of the Personal Overall experience with Efgartigimod in generalized Myasthenia gravis (POEMA) study, which aims to generate real-world data of efgartigimod treatment in patients with gMG.

An observational cohort of 100 adults in Italy with acetylcholine receptor antibody-positive gMG will be included. Efgartigimod treatment initiation will be decided independently of study participation as part of routine clinical care. The study will use prospective, retrospective, and administrative data from sources including patient medical records, caregiver and clinician questionnaires, administrative databases, and patient-reported outcomes (PROs; both validated and exploratory) selected in collaboration with patient advocacy groups. The primary objective is to describe overall and cycle-specific clinical impact of efgartigimod on Myasthenia Gravis Activities of Daily Living (MG-ADL) scores (including minimal symptom expression [MSE]).

Secondary objectives include patient quality of life, patient/clinician satisfaction, and gMG-related healthcare resource utilization/costs. Exploratory objectives include PROs, such as lived experience across life domains (work, daily functioning, family/social life, and physical discomfort), among others. Adverse events will be reported.

The POEMA study will contribute data from Italian clinical practice to provide a comprehensive understanding of how efgartigimod treatment in clinical settings affects individualized disease experience in patients with gMG.

MYASTHENIA

Abstract P113 - Cod. 142790

LONG-TERM SAFETY AND EFFICACY OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN ADULT PARTICIPANTS WITH GENERALIZED MYASTHENIA GRAVIS: FINAL RESULTS OF THE ADAPT-SC+ STUDY

Antozzi C.^{*1}, Bhavaraju--Sanka R.², De Bleecker J.L.³, Huang W.⁴, Jimenez R.H.⁴, Verhamme F.M.⁴, Liu L.⁴, Korobko D.⁵, Meisel A.⁶, Utsugisawa K.⁷, Vu T.⁸, Wiendl H.⁹, Howard Jr J.F.¹⁰

¹ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, United States of America, ³ Department of Neurology, Ghent University Hospital, Ghent, Belgium, ⁴ argenx, Ghent, Belgium, ⁵ State Budgetary Healthcare Institution of Novosibirsk Region "The State Novosibirsk Regional Clinical Hospital", Novosibirsk, Russian Federation, ⁶ Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany, ⁷ Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, ⁸ Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, United States of America, ⁹ Department of Neurology, Institute of Translational Neurology, University Hospital Münster, Münster, Germany, ¹⁰ Department of Neurology, The University of North Carolina, Chapel Hill, United States of America

Efgartigimod, a human immunoglobulin G1 (IgG1) Fc fragment, reduces IgG levels (including pathogenic autoantibodies) through neonatal Fc receptor blockade. During ADAPT-SC, efgartigimod PH20 SC demonstrated noninferior total IgG reduction to intravenous (IV) efgartigimod in participants with gMG. Participants completing ADAPT-SC or enrolled in ADAPT+ (efgartigimod IV open-label extension [OLE]) could enter the ADAPT-SC+ OLE study. ADAPT-SC+ evaluated long-term safety and efficacy of subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) in participants with generalized myasthenia gravis (gMG).

Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 once-weekly injections. Subsequent cycles were initiated based on clinical evaluation (Year 1, ≥ 4 weeks between cycles; Year 2 and onward, ≥ 1 week between cycles following protocol amendment). Safety was assessed using incidence and severity of adverse events. Clinical efficacy was assessed using Myasthenia Gravis Activities of Daily Living (MG-ADL) scores.

During ADAPT-SC+, 180 participants received ≥ 1 efgartigimod PH20 SC injection (mean [SD] study duration, 2.6 [0.9] years; 459.4 participant years of follow-up). Adverse events were predominantly

mild/moderate. Injection site reactions were mild/moderate, did not lead to discontinuation, and decreased in incidence with subsequent cycles. Efgartigimod remained well tolerated in participants whose cycle intervals shortened after Year 1. MG-ADL total score improvements in anti-acetylcholine receptor antibody-positive (AChR-Ab+) participants were observed by Week 1 and sustained through Week 163. 59.2% of AChR-Ab+ participants achieved minimal symptom expression (MG-ADL score, 0-1) at any time. Sustained improvements in quality-of-life measures were observed. Long-term treatment with efgartigimod PH20 SC was well tolerated and efficacious.

MYASTHENIA

Abstract P115 - Cod. 142970

MAKING THE INVISIBLE AUDIBLE: A REAL-WORLD CONNECTED SPEECH STUDY IN MYASTHENIA GRAVIS

D'Amico E.^{*}, Di Filippo P.S., Avolio C., Zanghi A.
university of foggia, foggia, Italy

Bulbar involvement in myasthenia gravis (MG) impairs voice and speech, yet subtle changes may be overlooked

We conducted a cross-sectional study of consecutively enrolled adults with confirmed MG at a single center. Participants completed standardized voice recordings and contemporaneous clinical assessments (Myasthenia Gravis–Activities of Daily Living [MG-ADL] and revised Myasthenia Gravis Quality of Life [rMG-QOL15]). Tasks included sustained vowels, standardized reading, and spontaneous speech.

Acoustic metrics comprised root-mean-square intensity (RMS, dB) and fundamental frequency (F0, Hz).

Seventeen patients were enrolled (median age 58 years; 52.9% female). Median MG-ADL was 6.0 and mean rMG-QOL15 was 16.6, with no significant correlation ($p = 0.09$, $p = 0.74$). Male participants exhibited significant intensity reductions in connected speech: reading (-3.22 dB, IQR -5.98 to -2.09 ; pBH

$= 0.031$; $r = 0.84$) and spontaneous speech (-5.46 dB, IQR -6.11 to -4.93 ; $pBH = 0.031$; $r = 0.84$). Female participants showed smaller, nonsignificant changes (≤ -2.2 dB; all $pBH > 0.7$). F0 shifts were modest and non-significant after correction. Across the cohort, MG-ADL

correlated with both RMS and F0 drops in unadjusted models but not after adjusting for sex. rMG-QOL15 showed no overall association, although females demonstrated a correlation between F0 drop and QOL burden ($p = 0.77$, $p = 0.014$).

Connected-speech

intensity decrements, particularly in males, represent a robust acoustic marker of bulbar involvement in MG not captured by patient-reported outcomes

MYASTHENIA**Abstract P117 - Cod. 143227****MINISTEN, CAPTURING DAILY VARIABILITY IN MYASTHENIA GRAVIS WITH A MINIMAL-BURDEN MOBILE DIARY**

Bosco L.¹, Bosco M.², Sorrenti B.¹, Scalabroni L.¹, Laurini C.^{*1}, Falzone Y.M.¹, Previtali S.C.¹

¹ San Raffaele Hospital, Milano, Italy, ² ULSS 2 Marca Trevigiana, Treviso, Italy

Myasthenia gravis (MG) is characterized by symptom fluctuations that are poorly captured by routine outpatient follow-up. Daily diaries are widely used in other fluctuating conditions (e.g., migraine) to quantify real-world variability and trends between visits.

To develop and preliminarily validate a low-burden, privacy-preserving smartphone diary to track daily MG symptom dynamics and derive proxy patient-reported outcomes.

We built a mobile diary inspired by migraine trackers and the streamlined "daily check-in" paradigm of native mobile health apps. Once per day, patients answer five brief questions and rate visual analogue scales (VAS) across five domains: swallowing, limb/axial strength, respiration, vision, and quality of life. Each question includes targeted checkbox items reflecting functional limitations. Checkbox data are aggregated on a weekly rolling window into two surrogate indices: a proxy MG-ADL and a proxy MG-QoL. All data remain stored locally on the patient's phone. In a pilot cohort of 10 MG patients, we assessed feasibility (adherence, completion time) and preliminary validity versus standard questionnaires.

Full adherence was high (median completion > 80%). Proxy MG-ADL showed strong internal consistency (Cronbach's $\alpha \approx 0.88$) and convergent validity with standard MG-ADL ($r \approx 0.82$). Proxy MG-QoL correlated strongly with established QoL instruments ($r \approx 0.79$). Domain VAS tracked functional impairment ($r \approx 0.70-0.85$) and provided greater granularity in detecting short-term trends.

A brief, daily MG diary can capture clinically relevant fluctuations with minimal burden, while maintaining privacy through local-only storage and patient-controlled export. Larger studies should evaluate responsiveness and clinically meaningful change thresholds.

MYASTHENIA**Abstract P119 - Cod. 143510****MYASTHENIA GRAVIS AND AUTO-ABS NEUTRALIZING TYPE I IFNS IN A PATIENT WITH CARTILAGE-HAIR HYPOPLASIA**

Fetta A.^{*3}, Rosain J.¹, Bastard P.¹, Moratti M.², Corsini C.³, Maillard A.¹, Puel A.⁴, Giannoccaro M.P.⁵, Di Pisa V.³, Lanari M.², Casanova J.L.¹, Conti F.², Cordelli D.M.³

¹ Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children; University Paris Cité, Imagine Institute; Pediatric Hematology-Immunology and Rheumatology Unit, Necker Hospital for Sick children, Assis, ² Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, ³ IRCCS

Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età Pediatrica; Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna., Bologna, Italy, ⁴ Laboratory of Human Genetics of Infectious Diseases, INSERM U1163, Necker Hospital for Sick Children, Necker Branch; Imagine Institute, Paris University., Paris, France, ⁵ IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

Myasthenia Gravis (MG) is an autoimmune disease, in most cases mediated by autoantibodies against the acetylcholine receptor (AChR) with thymic involvement. Auto-Abs neutralizing type I interferons (AAN-I-IFNs) are found in 30% of MG patients and can lead to severe COVID-19. Cartilage-hair hypoplasia (CHH) (OMIM #250250) is a rare autosomal recessive disorder caused by pathogenic variants in the RMRP gene, characterized by skeletal dysplasia and combined immunodeficiency. Immune dysregulation in CHH may predispose to systemic autoimmune manifestations; however, an association with MG or AAN-I-IFNs has not been reported to our knowledge.

To report a novel association between MG, AAN-I-IFNs, and CHH.

A 11-year-old girl, who developed a life-threatening SARS-CoV-2 infection requiring intensive care admission was found to have AAN-I-IFNs. Subsequent immunological investigations revealed combined immunodeficiency and polyautoimmunity (alopecia areata, autoimmune thyroiditis, and multiple autoantibody positivity). She later developed progressive fatigability, dysphagia, nasal speech, diplopia, and fluctuating weakness. A significant decrement (> 12%) on repetitive nerve stimulation and high-titer anti-acetylcholine receptor antibodies (AChR-ab) allowed the diagnosis of MG. Disease severity was relevant (worst QMG score: 21), with partial clinical control on pyridostigmine and oral steroids and ongoing intravenous immunoglobulin dependence (best QMG score: 6). Whole exome sequencing was performed and revealed the presence of a homozygous pathogenic variant in RMRP: 9-35657983-G-T NR_003051.4(RMRP):n.37C > A, establishing the diagnosis of CHH. To our knowledge, we report the first case of MG and AAN-I-IFNs in a patient with CHH-associated systemic polyautoimmunity. This association is particularly relevant for elucidating the pathomechanisms underlying pediatric AChR-ab-positive MG, as it provides molecular evidence of thymic loss of tolerance in CHH. These findings have important therapeutic implications, including hematopoietic stem cell transplantation as a potential curative strategy.

MYASTHENIA**Abstract P121 - Cod. 142961****NEUROPHYSIOLOGICAL BIOMARKER OF RESPONSE TO EFGARTIGIMOD IN MYASTHENIA GRAVIS: A PILOT STUDY**

Erra C.^{*1}, Di Stefano V.², Campo S.², Della Valle P.¹, Fasolino A.¹, Maggio B.², Ricciardi D.¹, Tuccillo F.¹, Brighina F.², Habetswallner F.¹

¹ Aorn A. Cardarelli, Neurophysiopathology Unit, Napoli, Italy, ² Neurology Unit, Department of Biomedicine, Neuroscience, and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy

Generalized myasthenia gravis (gMG) is an acquired autoimmune

pathology mediated by IgG directed against proteins of the post-synaptic membrane of the neuromuscular junction.

Efgartigimod competes with IgG for binding to the neonatal receptor for the crystallizable fragment (FcRn) which increases catalysis of pathogenic auto-IgG and was approved for gMG treatment in Europe in 2022.

Much attention has been lately directed to finding biomarkers which could predict or demonstrate response to the different drugs and therefore guide clinicians in choosing the best treatment as early as possible.

In this pilot study we aim to describe neurophysiological response in patients treated with efgartigimod in correlation to clinical response. Efgartigimod is administered by 4 endovenous weekly infusions in relation to AIFA criteria.

Clinical outcome was assessed through standardized clinical scales (MGADL, QMG) at the first and fourth week of treatment (respectively W1 and W4).

Neurophysiological response was investigated performing low frequency (3 Hz) repetitive nerve stimulation (RNS) at W1 and W4 in four standardized different muscular districts: nasalis, masseter, trapezius and abductor digiti minimi. Compound muscle action potential (CMAP) decrement was recorded in basal condition and 1, 2 and 3 minutes after voluntary activation.

Seventeen patients were included in the study.

A direct correlation between clinical improvement (MGADL and QMG score reduction) and neurophysiological improvement (reduction of decremental response) was registered.

Direct demonstration of neuromuscular transmission improvement through RNS is a promising biomarker for treatment response in gMG and further studies should be conducted in order to validate these results and assess feasibility.

MYASTHENIA

Abstract P123 - Cod. 143420

NEW TARGETED THERAPIES IN MYASTHENIA GRAVIS: ROLE OF MIR-150 AND MIR-146A AS PERSONALISED MEDICINE BIOMARKERS FOR MONITORING PATIENT RESPONSE

Berni A.*, Iacomino N., Frangiamore R., Tarasco M.C., Vanoli F., Farinazzo G., Marcuzzo S., Bonanno S., Maggi L., Mantegazza R., Antozzi C., Cavalcante P.

Fondazione IRCCS Istituto Neurologico Carlo Besta Neurology 4 – Neuroimmunology And Neuromuscular Diseases, Milan, Italy

Myasthenia gravis (MG) is an autoimmune disease characterized by muscle weakness and fatigability resulting from autoantibodies to neuromuscular junction (NMJ) components, mainly the acetylcholine receptor (AChR). Innovative targeted therapies, proven to be effective in clinical trials, are transforming the MG treatment landscape, promising to improve therapeutic success. Among them, efgartigimod (EFG) interferes with IgG recycling by blocking FcRn, while eculizumab (ECU) and ravulizumab (RAVU) prevent complement-mediated NMJ damage by targeting C5.

Moving beyond therapeutic efficacy, we investigated microRNAs

(miRNAs) as biomarkers of clinical response to targeted therapies.

By qPCR, we analysed MG-associated miRNAs (miR-150-5p, -21-5p, -423-5p, -146a-5p -30e-5p) in sera from 24 EFG-, 11 ECU- and 10 RAVU-treated AChR-MG patients at the following time points after baseline (T0): i) 4th infusion of cycle 2 (T1) and cycle 3 (T2) for EFG; ii) at 2 (T1) and 4 (T2) weeks for ECU; iii) at 2 weeks (T1) and 6 months (T2) for RAVU.

We observed a significant downregulation of miR-150-5p in both EFG- and ECU-treated patients at T2, while ECU- and RAVU-treated patients showed a significant upregulation of miR-146a-5p at T2, in line with disease improvement.

Since miR-150-5p and miR-146a-5p are key regulators of immune pathways, we suggest drug-related immunoregulatory effects beyond their known mechanisms of action, identifying these miRNAs as potential biomarkers to monitor and personalize targeted therapies in MG.

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MYASTHENIA

Abstract P125 - Cod. 143021

NON-CAPSULATED NEISSERIA MUCOSA SEPSIS IN A MG PATIENT TREATED WITH RAVULIZUMAB: CASE REPORT AND REVIEW OF THE LITERATURE

Rossini E.^{*1}, Tufano L.¹, Vera V.¹, Lauletta A.¹, Leonardi L.², Morino S.², Garibaldi M.¹, Antonini G.¹, Fionda L.²

¹ Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), SAPIENZA University of Rome, Rome, Italy., Rome, Italy,

² Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, Rome, Italy

Complement inhibitors increase susceptibility to infections caused by *Neisseria* species, particularly *Neisseria meningitidis*, making vaccination mandatory. Non-capsulated *Neisseria* species are usually commensals with limited virulence; however, invasive infections have been reported in both immunocompromised and immunocompetent individuals.

We report a case of *Neisseria mucosa* sepsis in a patient with acetylcholine receptor-positive (AChR+) thymoma-associated generalized myasthenia gravis (gMG) treated with ravulizumab. Additionally, a systematic literature review was conducted to identify reported invasive infections caused by uncommon *Neisseria* species in patients receiving complement inhibitors.

A 25-year-old woman with AChR+ thymoma-associated gMG was receiving ravulizumab every 8 weeks, azathioprine, and prednisone. She was fully vaccinated against *N. meningitidis* serogroups B and ACYW135. Seven weeks after her last ravulizumab infusion, she was hospitalized for febrile neutropenia, rapidly progressing to septic shock requiring vasoactive support. Blood cultures grew *Neisseria mucosa*. Azathioprine was discontinued, and she was successfully treated with intravenous ceftriaxone, achieving complete clinical

recovery. The literature review identified 10 additional cases of invasive infections caused by uncommon *Neisseria* species (*N. sicca*, *N. mucosa/subflava*, *N. cinerea*, *N. subflava*) in patients treated with complement inhibitors. Underlying conditions included MG, hemolytic uremic syndromes, paroxysmal nocturnal hemoglobinuria, and catastrophic antiphospholipid syndrome. Six patients were immunocompromised. Five developed sepsis and one septic shock. All recovered with antibiotic therapy.

Patients receiving complement inhibitors remain at risk for invasive infections caused by non-capsulated *Neisseria* species despite appropriate vaccination. Increased awareness and improved surveillance are needed to better define risk factors and preventive strategies.

MYASTHENIA

Abstract P127 - Cod. 143438

PATIENT ACCEPTABLE SYMPTOM STATE IN PATIENTS WITH MYASTHENIA GRAVIS TREATED WITH INNOVATIVE THERAPIES: A REAL-WORLD EXPERIENCE

Cheli M.*, Giacomuzzi Grigoli E., Salvucci G., Vanoli F., Antozzi C., Bonanno S., Frangiamore R., Maggi L.
Neurology 4 - Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

Patient Acceptable Symptom State (PASS) is a patient-centered outcome reflecting satisfactory symptom level. In myasthenia gravis (MG), PASS has been linked to thresholds in established clinical scales (MG-ADL, QMG, MGC, MGQoL15r), but never specifically evaluated in a large cohort of MG treated with innovative therapies (IT). We retrospectively analyzed PASS in MG patients treated with IT at our institution at multiple time points based on previously reported MG-ADL, QMG, MGC, and MGQoL15r cut-offs. The cohort included 101 patients (mean disease duration 12.1 years and 2.1 years of IT follow-up), 85 (84.2%) were AChR-Ab positive, 9 (8.9%) MuSK-Ab positive, and 7 (6.9%) seronegative. IT included efgartigimod (n = 43, 42.5%), rozanolixizumab (n = 9, 9.2%), zilucoplan (n = 8, 7.8%), eculizumab (n = 8, 7.8%), and ravulizumab (n = 33, 32.7%).

We found that patients whom reach the thresholds for MG-ADL, QMG, MGC and MGQoL15r were respectively 42%, 45%, 54.6% and 40.1% at 6 months, 45%, 46.7%, 56.7% and 40.6% at 1 year, 40%, 42.5%, 51% and 38% at 18 months and 43.5%, 42%, 58% and 46% at two-year follow-up. After 12 months, 15/64 (23.4%) of patients achieved PASS with full concordance across all four scales, and 9/39 (23.6%) after 24 months, without significant differences between patients reaching PASS and those who did not, and no differences between Fc-Rn-I or C5-i therapies. No significant associations were found between PASS status and demographic, antibodies status, clinical variables or treatment class.

PASS achievement appears feasible only in a subset of patients treated with IT, without a clinically significant increase over time.

MYASTHENIA

Abstract P129 - Cod. 143286

PATIENT CHARACTERISTICS, DOSING PATTERNS, AND OUTCOMES ASSOCIATED WITH INTRAVENOUS AND SUBCUTANEOUS EFGARTIGIMOD AMONG PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS IN CLINICAL PRACTICE

De Notariis A.*¹, Qi C.¹, Bhavaraju--Sanka R.², Smith A.G.³, Menon R.R.⁴, Zhang H.⁵, Sato M.⁵, Wolfe G.L.⁶

¹ argenx, Ghent, Belgium, ² Department of Neurology, University of Texas Health Science Center at San Antonio, San Antonio, United States of America, ³ Department of Neurology, Virginia Commonwealth University, Richmond, United States of America, ⁴ ZS Associates, Bengaluru, Karnataka, India, ⁵ ZS Associates, New York, New York, United States of America, ⁶ Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, Buffalo, United States of America

While clinical trials have demonstrated comparable safety and efficacy with intravenous (IV) and subcutaneous (SC) efgartigimod among adults with acetylcholine receptor antibody-positive (AChR-Ab+) generalized myasthenia gravis (gMG), data from clinical practice is limited. Here, we evaluate patient characteristics, dosing patterns, and outcomes among patients with gMG using IV or SC efgartigimod. Adults with gMG enrolled in the USA My VVGART Path patient support program by December 2024 who were treated with IV or SC efgartigimod were included. Patient characteristics and time between treatment cycles were analyzed. To assess outcomes, Myasthenia Gravis Activities of Daily Living (MG-ADL) before efgartigimod initiation was compared with best (lowest) MG-ADL captured after initiation at the patient-level.

Among 2878 patients who initiated efgartigimod after SC approval (July 2023), 69% (n = 1992) used only IV and 22% (n = 622) used only SC (9% used both and were excluded). Mean (SD) age and baseline MG-ADL was 65.8 (15.4) years and 8.1 (3.7) for IV, and 67.0 (15.3) years and 7.6 (3.4) for SC. Average (SD) efgartigimod cycles initiated was 2.9 (2.0) for IV and 2.3 (1.6) for SC. Four weeks was the most common gap between cycles for both formulations. For patients with MG-ADL available (IV: 862 [43%]; SC: 214 [34%]), mean (SD) best improvement from baseline was 5.4 (3.3) for IV and 4.8 (3.0) for SC.

Among patients with gMG, rapid and clinically meaningful outcomes were observed regardless of efgartigimod formulation, underscoring the value of formulation flexibility and administration options that can be tailored to patient preference.

MYASTHENIA

Abstract P131 - Cod. 142939

PATIENT-REPORTED EXPERIENCE WITH SUBCUTANEOUS ZILUCOPLAN IN GENERALIZED MYASTHENIA GRAVIS

MEASURED BY THE SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

Vinciguerra C.^{*1}, Di Stefano V.², Rini N.², Antozzi C.³, Liliana B.¹, Biasini F.⁴, Bisecco A.⁵, Bonanno S.³, Brighina F.², Codeluppi L.⁶, D'Alvano G.⁵, Damato V.⁷, D'Amico F.², Erra C.⁸, Fionda L.⁹, Habetswallner F.⁸, Maggi L.³, Meli A.², Pugliese A.⁴, Tuccillo F.⁸, Vanoli F.³, Vera V.¹⁰, Verza M.U.⁷, Frangiamore R.³

¹ Neurology Unit, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy, ² Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy, ³ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ⁴ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ⁵ Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Naples, Napoli, Italy, ⁶ Neurology Unit, Neuromotor & Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, ⁷ Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Firenze, Italy, ⁸ UOC Neurophysiopathology, AORN Cardarelli, Napoli, Italy, ⁹ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Roma, Italy, ¹⁰ Department of Neuroscience, Mental Health and Sensory Organs (NESMOS), SAPIENZA University of Rome, Roma, Italy

Subcutaneous (sc) self-administration of targeted-therapies may improve self-management and treatment-adherence in generalized-myasthenia gravis (gMG); however, disease-related muscle weakness, impaired dexterity, and injection-related anxiety may limit feasibility. The Self-Injection-Assessment-Questionnaire-2.0 (SIAQ2.0) is a validated patient-reported outcome measure designed to evaluate experiences with sc self-injection.

This study described patient experience with sc-zilucoplan in gMG using the SIAQ2.0 and explored changes over time.

Patients with gMG treated with sc-zilucoplan completed the SIAQ pre- and post-injection at different treatment weeks. Descriptive statistics summarized demographic and clinical characteristics and key SIAQ domains, including feelings about injections, self-confidence, pain and injection-site reactions, ease of use, embarrassment, and overall satisfaction. Correlation analyses assessed associations between treatment duration (weeks) and post-injection domain scores. Thirty-five patients (mean-age 55.8±16-yo; 19 female; mean disease-duration 113±91-months) were retrospectively enrolled across ten tertiary MG-referral-centers. SIAQ2.0 was collected over treatment-durations ranging from 24 to 86 weeks. At baseline, 15 patients (43%) reported moderate or greater fear or anxiety related to injections. During treatment, injection-related pain and local reactions were generally mild, with 8 (22%) reporting moderate or higher discomfort. Post-injection self-confidence was reported by 26 (73%), while embarrassment was infrequent in 5 (14.3%). Overall satisfaction with self-injection was reported by 32 (93 %). Treatment-duration correlated positively with self-confidence ($r = 0.50$, $p = 0.002$) and easy of use ($r = 0.51$, $p = 0.001$), negatively with injection-related pain and discomfort ($r = -0.43$, $p = 0.003$).

sc-Zilucoplan was well accepted by gMG patients, with increasing self-confidence and improved tolerability over time. The SIAQ2.0 supported the feasibility of self-injection in this population.

MYASTHENIA

Abstract P133 - Cod. 143193

PERCEIVED CARE NEEDS IN PATIENTS WITH MYASTHENIA GRAVIS: A CROSS-SECTIONAL STUDY USING A NURSING DISEASE-SPECIFIC QUESTIONNAIRE

Pastore F.^{*1}, Scognamiglio P.², Saba G.³, Catania D.⁵, Campanella A.⁴, Trovato M.⁶, Niccolai E.⁷, De Cristofaro M.⁷, Poloni P.⁸, Andreone G.⁹, Di Costanzo D.⁹, Carrara R.⁸, Oneta A.G.¹⁰, Rapetti A.¹⁰, Lorenzi R.¹¹, Fortunati F.¹², Vernarecci M.¹², Maccarelli M.¹³, Betteghella F.¹⁴, Marella P.¹⁴, Morra A.¹⁵, Domenicone E.¹⁶

¹ Department of Precision and Regenerative Medicine and Ionian Area (DiMePre-J), University of Bari Aldo Moro, Bari, Italy, Bari, Italy, ² U.O.C. Neurologia, Azienda Ospedaliero Universitaria Sant'Andrea, Roma, Italy, Rome, Italy, ³ Day Hospital Neurologia, Azienda Ospedaliera Brotzu, Cagliari, Italy, Cagliari, Italy, ⁴ SSD Neurologia Ricerca e Sviluppo Clinico, IRCCS Fondazione Istituto Neurologico Carlo Besta, Milano, Italy, Milano, Italy, ⁵ DH Neuroscienze, Azienda Città della Salute e della Scienza di Torino, Presidio Molinette, Torino, Italy, Torino, Italy, ⁶ Centro di Riferimento Regionale per le Malattie Neuromuscolari, Sicilia Occidentale, Italy, Palermo, Italy, ⁷ DH Neurologia, AOU Careggi, Firenze, Italy, Firenze, Italy, ⁸ Neurologia MAC, ASST Papa Giovanni XXIII, Bergamo, Italy, Bergamo, Italy, ⁹ UOC I Neurologia, AOU Vanvitelli, Napoli, Italy, Napoli, Italy, ¹⁰ Ambulatorio Neurologia, IRCCS Ospedale Policlinico San Martino, Genova, Italy, Genova, Italy, ¹¹ Azienda Sanitaria Siracusa, Siracusa, Italy, Siracusa, Italy, ¹² AOU delle Marche, Ancona, Italy, Ancona, Italy, ¹³ DS/DH Neurologia, ASL Toscana Centro, Ospedale Santo Stefano, Prato, Italy, Prato, Italy, ¹⁴ DH/DS Neurologia, AOUI Verona, Ospedale Borgo Roma, Verona, Italy, Verona, Italy, ¹⁵ DH Neurofisiopatologia, AORN Cardarelli, Napoli, Italy, Napoli, Italy, ¹⁶ ASL ROME 1, ROMA, Italy

Myasthenia Gravis (MG) is a chronic neuromuscular disorder characterized by fluctuating symptoms that require continuous care and patient support. However, patients' perceived care needs during treatment and follow-up remain poorly described, and nursing contributions to these needs are not fully explored.

To assess perceived care needs in patients with MG and to explore the role of nursing support and clinical variables associated with these needs. A cross-sectional study was conducted involving 115 patients with MG. Participants completed a 20-item nursing questionnaire on perceived care needs, the MG-QOL15, and additional items assessing perceived nursing support. Descriptive statistics were calculated. A multivariable linear regression model was performed to identify predictors of perceived care needs. Participants had a mean age of 52.8 ± 15.5 years; most had generalized MG (85.2%). The mean perceived care needs score was 59.2 ± 21.4 (range 20–100), while the mean MG-QOL15 score was 20.8 ± 12.9 . In multivariable analysis ($R^2 = 0.342$), perceived nursing support was the only significant predictor of higher perceived care needs ($\beta = 9.48$, $p < .001$), whereas age, disease duration, MG-QOL15, and follow-up in a specialized center were not associated with the outcome.

Perceived nursing support emerged as the main factor associated with patients' perceived care needs in MG. These findings highlight the central role of nursing in supporting patients throughout the disease trajectory and underline the importance of structured nursing interventions to address unmet care needs.

MYASTHENIA

Abstract P135 - Cod. 143465

PREVALENCE AND PREDICTORS OF SLEEP DISTURBANCES IN AN ITALIAN COHORT OF PATIENTS WITH MYASTHENIA GRAVIS

Iovino V.^{*}, Colitta A., Cepele A., Lo Iacono A., Guida M., Maestri Tassoni M.

Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy

Previous studies have reported a high prevalence of sleep disturbances in myasthenia gravis (MG) patients (24% to 64%), while the relationship between sleep abnormalities and MG-related outcomes remains unclear.

The aims of this study were to assess the prevalence of self-reported sleep disturbances and to explore potential associations between sleep parameters and MG outcome measures in a cohort of MG patients.

A battery of validated self-report questionnaires assessed sleep disorders (PSQI, rMEQ, ESS, BQ, ISI, RLS screen, RBD1Q), anxiety and depression (HADS) and fatigue (FSS). Demographic and clinical data (MG subtype and MGFA classification) were obtained from medical records. MG-related functional status, quality of life, and clinical severity were evaluated using MG-ADL, MG-QoL-15r, and MGC.

Descriptive statistics were computed, and multivariate linear or binomial models examined associations between sleep parameters and MG outcome measures, including one MG variable per model to avoid multicollinearity.

100 patients with MG were enrolled (mean age 50 years; mean BMI 28.9; 64 females). Sleep disturbances were highly prevalent, including poor sleep quality (93%), insomnia (36%), excessive daytime sleepiness (13%), high risk of obstructive sleep apnea (19%), and symptoms of restless legs syndrome and REM sleep behavior disorder (44% and 15%).

In regression models, ESS was predicted by MGC ($p = 0.014$) and MG-ADL ($p = 0.024$), high pre-test OSAS risk was predicted by MG-ADL ($p = 0.021$) and BMI ($p = 0.002$). Furthermore, MG-ADL predicted RLS ($p = 0.005$).

Finally, all MG outcome measures predicted fatigue severity.

Self-reported sleep disturbances were common in this MG cohort and showed distinct associations with disease outcome measures, independent of demographic and clinical factors, suggesting that routine sleep assessment may enhance MG management and patient well-being.

MYASTHENIA

Abstract P137 - Cod. 143394

RADIATION-INDUCED MOTOR NEURON DISEASE MIMICKING MYASTHENIA GRAVIS: A CASE REPORT

Pauro A.^{*}, Capece G.¹, Sogus E.², Petrosino A.², Fornasier T.²,

Bello L.², Pegoraro E.², Sorarù G.², Minicuci G.M.³

¹ *Dipartimento di Neuroscienze, Azienda Ospedale Università Padova, Padova, Italy*, ² *Department of Neurosciences, University of Padova, Padova, Italy*, ³ *Clinica Neurologica, Padova University Hospital, Padova, Italy*

Radiation-induced motor neuron disease (RIMND) is a rare, atypical motor neuron disorder developing months to years after radiation therapy, usually with total doses of 5000–6000 rad. It is clinically characterized by progressive weakness, marked muscle atrophy, and fasciculations.

We report a case of RIMND after radiotherapy for B1 thymoma, with anti-acetylcholine receptor (anti-AChR) antibody positivity.

A 57-year-old woman diagnosed with B1 thymoma in 2021 underwent chemotherapy, which was discontinued due to paresthesias and EMG evidence of polyneuropathy, followed by high-dose radiotherapy. Her history included IgG kappa monoclonal gammopathy of undetermined significance (MGUS) and paroxysmal atrial fibrillation treated with amiodarone. In 2025, she was re-evaluated for a two-year history of progressive neck extensor weakness, resulting in dropped head syndrome, and occasional subjective dysphagia. She had no ocular or limb weakness. Neurological examination revealed marked atrophy of cervical muscles and part of the shoulder girdle. Anti-AChR antibodies were markedly elevated (> 9 nmol/L), although such antibodies have been described in thymoma patients without myasthenia gravis (MG). Anticholinesterase therapy produced no clinical benefit. Follow-up EMG showed no neuropathy; repetitive nerve stimulation at 3 Hz was negative, including proximal muscles. Needle EMG demonstrated neurogenic changes, with fasciculations and myokymia in cervical paraspinal muscles. A diagnosis of post-radiation motor neuron disease was made.

This case illustrates the diagnostic challenge of anti-AChR positivity with dropped head syndrome, which may mimic MG. However, EMG findings and lack of response to anticholinesterase therapy supported the diagnosis of RIMND.

MYASTHENIA

Abstract P139 - Cod. 143370

REAL-WORLD EXPERIENCE WITH SUBCUTANEOUS EFGARTIGIMOD: A SINGLE-CENTER STUDY

Falso S.^{*}, Marini S., Marini M., Habetswallner F., Iorio R.

Department of Neuroscience, Catholic University of the Sacred Heart, Roma, Italy

Efgartigimod is a neonatal fragment crystallizable receptor (FcRn) antagonist approved for the treatment of generalised myasthenia gravis (gMG) in adults with anti-acetylcholine receptor antibodies (AChR-Ab). Efgartigimod is available in both intravenous (IV) and subcutaneous (SC) formulations. In a phase III trial, SC efgartigimod was non-inferior to IV efgartigimod in reducing total immunoglobulin G levels, with comparable clinical benefit. However, real-world experience with SC efgartigimod remains limited.

We enrolled AChR-MG patients treated with SC efgartigimod at our center. Baseline characteristics, clinical efficacy, and patients' sat-

isfaction were collected. Myasthenia Gravis–Activities of Daily Living (MG-ADL) and Quantitative Myasthenia Gravis (QMG) scales were used to assess clinical efficacy. Satisfaction was investigated through 9-item Treatment Satisfaction Questionnaire for Medication (TSQM-9).

Twenty AChR-MG patients were included, 40% were female. Median age at onset was 48 (range 15–78). Nine patients (45%) had thymoma. Eleven patients (55%) switched from IV Efgartigimod. After the first SC cycle, MG-ADL improved by -3.35 (-1 , -10 ; $p < 0.0001$) and QMG by -4.60 (0 , -14 ; $p = 0.0001$). Twelve patients (60%) achieved minimal symptom expression (MSE). TSQM-9 scores (0 – 100) showed high perceived effectiveness and convenience (mean $\pm$ SD: 72.7 ± 23.9 and 71.4 ± 21.8 , respectively), whereas global satisfaction was moderate (54.6 ± 23.4) ($n = 15$).

SC efgartigimod was associated with significant reductions in MG-ADL and QMG and a high rate of patients achieving MSE after the first cycle. Larger studies with longer follow-up and comparative analyses versus IV treatment, are warranted to better define the role of SC efgartigimod in routine clinical care.

MYASTHENIA

Abstract P141 - Cod. 143064

REPEATED CYCLES OF ROZANOLIXIZUMAB TREATMENT IN PATIENTS WITH ANTI-MUSCLE-SPECIFIC TYROSINE KINASE ANTIBODY-POSITIVE GENERALISED MYASTHENIA GRAVIS

Rossini E.^{*1}, Druzdz A.², Habib A.³, Lange D.⁴, Mantegazza R.⁵, Naito H.⁶, Pascuzzi R.⁷, Sacconi S.⁸, Utsugisawa K.⁹, Vissing J.¹⁰, Vu T.¹¹, Yeh J.¹², Grimson F.¹³, Pulido--Valdeolivas I.¹⁴, Tarancón T.¹⁴, Bril V.¹⁵

¹ Department of Neurology, Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy, ² Department of Neurology, Municipal Hospital, Poznań, Poland, ³ MDA ALS & Neuromuscular Center, Department of Neurology, University of California, Irvine, Orange, CA, United States of America, ⁴ Lange Neurology, New York, NY, United States of America, ⁵ Emeritus and Past Director, Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS, Istituto Nazionale Neurologico Carlo Besta, Milan, Italy, ⁶ Department of Clinical Neuroscience and Therapeutics, Hiroshima University, Hiroshima, Japan, ⁷ Neurology Department, Indiana University School of Medicine, Indiana University Health, Indianapolis, IN, United States of America, ⁸ Université Côte d'Azur, Peripheral Nervous System & Muscle Department, Pasteur 2 Hospital, Centre Hospitalier Universitaire de Nice, Nice, France, ⁹ Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, ¹⁰ Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, ¹¹ Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, United States of America, ¹² Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan, ¹³ UCB, Slough, United Kingdom, ¹⁴ UCB, Madrid, Spain, ¹⁵ Ellen and Martin Prosserman Centre for Neuromuscular Diseases, Toronto General Hospital, University of Toronto, Toronto, Canada

MycarinG (Phase 3, MG0003/NCT03971422) demonstrated efficacy of six once-weekly rozanolixizumab infusions versus placebo

in adults with generalised myasthenia gravis (gMG). Patients could then enrol in open-label extensions MG0004 (NCT04124965) then MG0007 (NCT04650854), or MG0007 directly.

Here, we evaluate the efficacy and safety of repeated rozanolixizumab cycles in patients with anti-muscle-specific tyrosine kinase antibody-positive (anti-MuSK Ab+) gMG. In MG0004, patients received once-weekly rozanolixizumab infusions for ≤ 52 weeks. In MG0007, following an initial rozanolixizumab cycle, subsequent cycles were administered upon symptom worsening (investigator's discretion). Final rozanolixizumab data (7 mg/kg and 10 mg/kg) were pooled across MycarinG, MG0004 (first 6 weeks) and MG0007 for patients with ≥ 2 symptom-driven cycles (efficacy) and MycarinG/MG0007 for patients with ≥ 1 treatment cycle (safety). Efficacy outcomes included change from baseline (CFB) to Day 43 in each cycle for myasthenia gravis (MG)-specific scores.

Overall, 12/129 patients who received ≥ 2 symptom-driven rozanolixizumab cycles had anti-MuSK Ab+ gMG. Across Cycles 1–9, mean (standard deviation) CFB in MG-Activities of Daily Living score ranged from -3.0 (3.6; Cycle 5, $n = 8$) to -7.0 (3.5; Cycle 1, $n = 12$). Mean CFB in MG Composite and Quantitative MG scores ranged from -5.8 (7.4; Cycle 9, $n = 5$) to -13.9 (6.6; Cycle 1, $n = 12$) and -5.2 (1.9; Cycle 8, $n = 5$) to -10.6 (6.0; Cycle 3, $n = 8$), respectively. Treatment-emergent adverse events occurred in 14/18 (77.8%) patients with anti-MuSK Ab+ gMG who had ≥ 1 treatment cycle; most were mild/moderate.

Rozanolixizumab efficacy in patients with anti-MuSK Ab+ gMG was maintained over repeated treatment cycles, with an acceptable safety profile. Funding: UCB.

MYASTHENIA

Abstract P143 - Cod. 143474

SEMI-QUANTITATIVE ANTI-ACHR ANTIBODY DETECTION USING FIXED CELL-BASED ASSAY (CBA). ASSOCIATION WITH CLINICAL SEVERITY AND NEUROPHYSIOLOGICAL IMPAIRMENT IN MYASTHENIA GRAVIS

Brienza M.^{*1}, Ceccanti M.², Cortese F.¹, Cuomo L.³, De Giglio L.¹, Pennisi E.M.¹

¹ Neurology Unit, Neuromuscular and Rare Neurological Diseases Center, San Filippo Neri Hospital, ASL RM1, Rome, Italy, ² Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, ³ U.O.C. Clinical Pathology, San Filippo Neri Hospital, ASLRoma1, Rome, Italy., Rome, Italy

The clinical significance of AChR-Ab titres remains complex. Across patients, absolute antibody levels show inconsistent correlation with disease severity.

To employ fixed cell-based assay (CBA) as a semi-quantitative technique for the detection of anti-AChR and anti-MuSK antibodies in patients with myasthenia gravis (MG). To investigate the relationship between semi-quantitative fCBA, clinical severity and electrophysiological data.

We conducted a retrospective study involving 22 patients with MG. Patients received MG diagnosis and have been clinically and electrophysiologically characterized with repetitive nerve stimulation. For

fCBA we used serial twofold dilutions, from 1:10 to 1:1280, until the highest dilution demonstrating specific membrane fluorescence. Lower Ab dilution was found in ocular vs generalized MG with a trend for significance (mean 2,2 vs 2,8; $p = 0.118$ Mann-Whitney U test). Electromyography data were available for 16/22 patients. We did not find a significant correlation between CMAP decrement and dilution. Antibody titres tended to be higher in patients with thymic pathology, showing a moderate effect size despite not reaching statistical significance.

Our study is the first assessing semiquantitative fCBA. Although our sample is too small to establish reliable statistical analyses, antibody titres showed a trend toward association with disease phenotype, with higher levels observed in generalized forms, but with no statistical significance. While cross-sectional correlations is inconsistent, longitudinal antibodies quantification in single patients with semi-quantitative fixed CBA could provide further information in disease monitoring, complementing clinical and electrophysiological assessment.

MYASTHENIA

Abstract P145 - Cod. 142985

SENSITIVITY OF REPETITIVE NERVE STIMULATION IN MYASTHENIA GRAVIS: DIAGNOSTIC YIELD AND DISEASE EXPRESSION

Rini N.*, Baiamonte L., Lo Mauro E., D'Amico F., Lupo M., Lima S.M., Quartetti U., Brighina F., Di Stefano V.

Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy

Repetitive nerve stimulation (RNS) plays an important role in the diagnostic workup of myasthenia gravis (MG), although its sensitivity in routine clinical practice is known to be limited. Strategies to improve the diagnostic yield of RNS are therefore needed.

This study aimed to evaluate the diagnostic performance of RNS in a real-world setting, focusing on the impact of the number and distribution of stimulation sites and on correlations between neurophysiological findings and clinical measures.

We conducted a retrospective study including 281 patients referred for suspected MG who underwent RNS at a tertiary neuromuscular center between 2015 and 2025. RNS showed high specificity (96.3%) whereas sensitivity was lower (49.5%). Sensitivity increased with the number of stimulation sites examined, being 44.8% with single-site protocols and 58.1% when two or more sites were tested, while specificity remained consistently high. Proximal and bulbar muscles showed higher diagnostic yield than distal muscles. Amplitude decrement significantly differed between RNS-positive and RNS-negative subjects for nasalis and trapezius muscles, but not for the abductor digiti minimi. In contrast, CMAP area reduction was significant for trapezius and abductor digiti minimi and correlated with selected MG Activities of Daily Living subscores.

RNS retains high diagnostic specificity, while its sensitivity can be improved by adopting a multi-site stimulation approach. Combining proximal and distal muscle testing enhances diagnostic accuracy and

provides complementary neurophysiological information that may also reflect disease burden.

MYASTHENIA

Abstract P147 - Cod. 142973

SEQUENTIAL AUTOIMMUNE MANIFESTATIONS IN THYMOMA: MYASTHENIA GRAVIS, FOCAL MYOSITIS, AND LIMBIC ENCEPHALITIS

Rossi P.*, Torchia E., Cicia A., Carlomagno V., Di Marco C., Marchese D., Habetswallner F., Falso S., Marini S., Iorio R., Lucchini M., Mirabella M.

Fondazione Policlinico Gemelli IRCCS, Roma, Italy

The association between thymic tumors and autoimmune disorders -particularly myasthenia gravis (MG)- is well recognized; however, the occurrence of multiple concomitant paraneoplastic syndromes remains exceedingly rare.

We present the case of a patient with thymoma who developed autoimmune diseases involving the peripheral and central nervous systems.

A 58-year-old woman, with a history of thymoma diagnosed in 2018, presented in May 2023 with subacute, fluctuating dysphagia, followed weeks later by weakness of left hand and finger extensors. Serum creatine phosphokinase (CPK) was mildly elevated (415 U/L) and anti-acetylcholine receptor antibodies were positive. Needle electromyography of distal upper limb extensor muscles showed myopathic changes with spontaneous activity. MG associated with focal inflammatory myopathy was diagnosed.

The patient underwent thymectomy and received one cycle of intravenous immunoglobulins (IVIg), pyridostigmine, and corticosteroids, resulting in resolution of dysphagia but only minimal improvement of distal weakness. At six-month follow-up, persistent atrophy and weakness of the left wrist and finger extensors were observed, with CPK normalization.

In August 2025, the patient developed subacute neuropsychiatric symptoms. Brain MRI showed bilateral limbic involvement, predominantly in the right temporal lobe, supported by electroencephalographies abnormalities. Serum anti-collapse response mediator protein 5 (CRMP5) antibodies were positive, leading to a diagnosis of autoimmune limbic encephalitis. Treatment with IVIg and corticosteroids, followed by resulted in rapid clinical and radiological improvement.

This case highlights a thymoma-associated autoimmune overlap syndrome with sequential involvement of the neuromuscular junction, skeletal muscle, and central nervous system, supporting a model of thymoma-driven immune dysregulation with progressive epitope spreading.

MYASTHENIA

Abstract P149 - Cod. 142701

SUSTAINED CLINICAL BENEFIT WITH LIMITED RETREATMENT: REAL-WORLD EXPERIENCE

WITH EFGARTIGIMOD IN ACHR-POSITIVE GENERALIZED MYASTHENIA GRAVIS

D*Alvano G.*, D'Anna F., Marigliano D., Capuozzo F., Sansone R., Todisco V., Tessitore A., Bisecco A.
Department of Advanced Medical and Surgical Sciences – University of Campania “Luigi Vanvitelli”, Napoli, Italy

Efgartigimod is a humanized IgG1 Fc fragment acting as a neonatal Fc receptor (FcRn) antagonist, approved as add-on therapy for AChR-positive generalized myasthenia gravis (gMG). Aim of this study was to evaluate the real-world effectiveness and safety of efgartigimod in a cohort of AChR+ gMG patients.

All AChR+ gMG patients treated with efgartigimod at our centre were included. MG-ADL and QMG scores were assessed at baseline and at the end of each cycle. MG-ADL was additionally monitored by telephone every two weeks to guide retreatment (sustained worsening ≥ 2 points). Safety and efficacy outcomes were recorded.

Seven patients (5 females; median disease duration 78 months) were analysed. Mean follow-up duration was 55.1 ± 23.3 weeks. Annualized cycle rate was 1.75: five patients received two cycles, only one required a third. Mean interval between first and second cycle was 20.6 weeks. Significant improvements were observed after each cycle: mean MG-ADL decreased from 6 to 2.4 after the first cycle and from 3.8 to 2 after the second; mean QMG improved from 9.4 to 5.9 and from 8.4 to 6, respectively. No acute exacerbations or adverse events were observed.

In our cohort, efgartigimod was associated with rapid and sustained clinical improvement and excellent safety profile. The limited number of treatment cycles may reflect the relatively low disease severity at baseline and the close clinical monitoring allowing early intervention. These findings are consistent with the efficacy and durability reported in the ADAPT trial and support the use of efgartigimod in tightly monitored clinical practice.

MYASTHENIA

Abstract P151 - Cod. 143051

SUSTAINED LONG-TERM RESPONSE TO EFGARTIGIMOD IN ACHR+ GMG FOLLOWING ANTI-COMPLEMENT THERAPY DISCONTINUATION: A CASE REPORT

Pisano G.*, Manca D., Cossu G.
ARNAS G. BROTTZU, Cagliari, Italy

Generalized myasthenia gravis (gMG) associated with acetylcholine receptor antibodies (AChR+) is a chronic autoimmune neuromuscular disorder requiring long-term immunomodulatory therapy. Complement inhibitors are effective in refractory disease but may increase infection risk, particularly in patients with multiple comorbidities. Efgartigimod, an FcRn antagonist, offers a targeted alternative by reducing pathogenic IgG levels. Data on treatment switching and long-term outcomes in real-world clinical practice remain limited.

To describe a real-world case of AChR+gMG with multiple cardiovascular and autoimmune comorbidities, highlighting the clinical rationale for switching from complement inhibitors to efgartigimod, and

to evaluate long-term efficacy and safety following anti-complement therapy discontinuation.

A 67-year-old male patient with AChR+ gMG and psoriatic arthritis with severe cardiovascular comorbidities, including aortic valve stenosis treated with bioprosthetic replacement, myocardial infarction with coronary revascularization, peripheral arterial disease, and pericardial effusion requiring drainage. After azathioprine failure and discontinuation of eculizumab/ravulizumab due to bilateral infected leg ulcers (*Klebsiella pneumoniae*), efgartigimod was initiated in August 2025, leading to an exceptionally prolonged and sustained clinical response without further severe infections, maintained until mid-January 2026.

This case highlights efgartigimod as an effective and safe therapeutic option in complex AChR+ gMG patients requiring anti-complement therapy discontinuation. The exceptionally prolonged clinical response observed supports FcRn blockade as a valuable long-term strategy, even in patients with significant cardiovascular and autoimmune comorbidities and increased infection risk.

MYASTHENIA

Abstract P153 - Cod. 143007

SUSTAINED MINIMAL SYMPTOM EXPRESSION IN GENERALISED MYASTHENIA GRAVIS: A 120-WEEK POST HOC ANALYSIS OF RAISE-XT

Marini S.*¹, Bresch S.², Freimer M.³, Hewamadduma C.⁴, Juntas-Morales R.⁵, Leite M.I.⁶, Maniaol A.⁷, Utsugisawa K.⁸, Vu T.⁹, Weiss M.¹⁰, Boroojerdi B.¹¹, Grimson F.¹², Savic N.¹³, Howard J.¹⁴

¹ Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ² Service de Neurologie, Hôpital Pasteur, Centre Hospitalier Universitaire de Nice, Nice, France, ³ Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, United States of America, ⁴ Academic Neuromuscular Unit, Sheffield Teaching Hospitals NHS Foundation Trust & Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, United Kingdom, ⁵ Department of Neurology, Vall d'Hebron University Hospital, Barcelona, Spain, ⁶ Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom, ⁷ Department of Neurology, Oslo University Hospital, Oslo, Norway, ⁸ Department of Neurology, Hanamaki General Hospital, Hanamaki, Japan, ⁹ Department of Neurology, University of South Florida Morsani College of Medicine, Tampa, FL, United States of America, ¹⁰ Department of Neurology, University of Washington Medical Center, Seattle, WA, United States of America, ¹¹ UCB, Monheim, Germany, ¹² UCB, Slough, United Kingdom, ¹³ UCB, Bulle, Switzerland, ¹⁴ Department of Neurology, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States of America

Minimal symptom expression (MSE), defined as a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of 0 or 1, is a rigorous measure of therapeutic efficacy in myasthenia gravis (MG).

This post hoc analysis of RAISE-XT (NCT04225871), a Phase 3, open-label extension study of the complement component 5 inhibitor zilucoplan, assessed the durability of MSE response. Adults with anti-acetylcholine receptor antibody-positive generalised MG who completed a qualifying double-blind, placebo-controlled study (NCT03315130/NCT04115293 [RAISE]) could opt to enter RAISE-XT and self-administer once-daily subcutaneous injections of zilucoplan

0.3mg/kg. The cumulative proportion of patients who achieved MSE (MG-ADL score of 0 or 1 without rescue therapy) at any time during zilucoplan treatment up to Week 120 and the proportion of time spent in MSE up to Week 120 were assessed post hoc (interim data cut-off: 11 November 2023).

Of 200 patients enrolled in RAISE-XT, 183 received zilucoplan 0.3mg/kg or placebo in the double-blind studies. The cumulative proportion of patients who achieved MSE at any time from the start of zilucoplan treatment up to Week 120 in the zilucoplan 0.3mg/kg/zilucoplan 0.3mg/kg and placebo/zilucoplan 0.3mg/kg groups was 61% and 64%, respectively. After first achieving MSE during zilucoplan treatment, patients maintained their MSE response for a median (range) of 80.8% (0.8–100.0%) of their remaining time in the study up to Week 120. Treatment-emergent adverse events were experienced by 97.0% (n = 194/200) of patients; most were mild or moderate. Zilucoplan demonstrated sustained efficacy, as shown by maintenance of MSE response up to 120 weeks of treatment. Funding: UCB.

MYASTHENIA

Abstract P155 - Cod. 142947

THE IMPACT OF TEMPERATURE IN MYASTHENIA GRAVIS: A REAL-LIFE CORRELATION STUDY BETWEEN ENVIRONMENTAL AND BODY TEMPERATURE WITH DISEASE ACTIVITY

Di Martino G.^{*1}, Mineo M.¹, Maccora S.¹, D'Anniballe F.¹, Eroe G.G.¹, Meli A.¹, D'Amico F.¹, Rini N.¹, Mondelli M.C.², Petrone M.², De Maio M.M.², Bevilacqua L.², Vinciguerra C.², Brighina F.¹, Di Stefano V.¹

¹ Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo, Palermo, Italy, ² Neurology Unit, Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy

Myasthenia Gravis (MG) is an autoimmune disease that affects the neuromuscular junction at the postsynaptic membrane. It is known that temperature affects signal transmission at the neuromuscular junction. However, the literature lacks real-life studies examining the actual clinical impact of environmental and body temperature on the MG symptoms.

In this real-life study we investigated the correlation between environmental and body temperature and clinical disease activity in myasthenic patients. Body temperature was measured using a laser thermometer; the external temperature was taken from a weather app; while a temperature monitoring sensor was used to measure room temperature. Each enrolled patient was administered clinical assessment scales such as Myasthenia Gravis Activity of Daily Living (MG-ADL), Myasthenia Gravis Composite (MGC), and Myasthenia Gravis Quantitative (QMG). Temperatures were recorded at the time of the clinical visit along with the assessment scales.

107 patients with Myasthenia Gravis were enrolled. Correlation analyses, conducted using Spearman's test, showed a positive and statistically significant correlation between clinical rating scale scores (MG-ADL, QMG, MGC) and patient body temperature. The correlation

between clinical scale scores and environmental temperature did not reach statistical significance, although scatterplots suggest a positive trend.

The data emerging from our study highlight a possible correlation between increased temperature, particularly body temperature, and clinical disease activity. These findings underscore the relevant role of patient education and the adoption of targeted behaviours in symptom control. Further studies, with larger sample sizes, are needed to confirm these results obtained from our real-life experience.

MYASTHENIA

Abstract P157 - Cod. 143498

THE ROLE OF ZILUCOPLAN IN THE MANAGEMENT OF REFRACTORY MYASTHENIC CRISIS: REPORT OF FIRST TWO ITALIAN CASES

Bevilacqua L.^{*1}, Erra C.², Ricciardi D.², Tuccillo F.², Habetswallner F.², Pellecchia M.T.³, Barone P.³, Vinciguerra C.¹

¹ Neurology Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy, ² Clinical Neurophysiology Unit, Azienda Ospedaliera di Rilievo Nazionale-Antonio Cardarelli, Naples, Italy, ³ Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", Neuroscience Section, University of Salerno, Salerno, Italy

Complement inhibition has emerged as a game-changing approach for the treatment of acetylcholine receptor (AChR) antibody-positive myasthenia gravis (MG), including Myasthenic Crisis (MC). Zilucoplan is a subcutaneous macrocyclic peptide C5-inhibitor. To date, evidence of effectiveness in the acute settings remains limited.

We report two AChR-positive MG patients with severe, treatment-refractory exacerbations—one in true MC and the other in impending crisis—who received zilucoplan 32.4 mg/day subcutaneously after failure of corticosteroids, intravenous immunoglobulin (IVIg), and prior biologic therapies.

The first patient, a 38-year-old man with thymoma-associated MG unresponsive to intravenous immunoglobulins (IVIg), steroids, steroid-sparing immunosuppressants, and multiple biologics including other complement inhibitors, who experienced marked bulbar and respiratory recovery within one week of zilucoplan initiation, allowing withdrawal from non-invasive ventilation and resumption of oral feeding. The second, an 81-year-old man with impending respiratory failure and severe bulbar dysfunction, showed complete resolution of dysphagia and dysphonia within 10 days avoiding hospitalization and ventilatory support. Both patients maintained sustained remission with no adverse events under ongoing zilucoplan therapy.

Zilucoplan provided rapid, robust, and durable improvement in refractory AChR-positive MG during MG and impending crisis. Larger prospective studies are warranted to define optimal use and timing of zilucoplan in MG crisis management.

MYASTHENIA

Abstract P159 - Cod. 142662**ZILUCOPLAN AS A THERAPEUTIC OPTION IN REFRACTORY MYASTHENIA GRAVIS COMPLICATED BY MYASTHENIC CRISIS**

Benedetti M.^{*1}, Mazzoli M.¹, Frangiamore R.², Galassi G.¹, Ariatti A.¹

¹ Department of Biochemical, Metabolic and Neural Sciences, University of Modena & Reggio Emilia, Italy, Modena, Italy, ² Department of Neurology 4 – Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, Milano, Italy

Myasthenic crisis (MC) is a rapid clinical decline observed in patients with Myasthenia Gravis (MG), requiring non-invasive (NIV) or mechanical ventilation (MV). Zilucoplan is a peptide binding to C5 protein of complement system, impeding formation of membrane attack complex. Recent reports described use of zilucoplan in refractory MG patients and MC.

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In 2019, a 62-year-old man was diagnosed having generalized MG with positive anti-acetylcholine receptor antibodies, associated with B2-thymoma treated with surgery, followed by radiotherapy and chemotherapy. Over 5 years he received immunosuppressants, including azathioprine, mychophenolate, courses of intravenous immunoglobulin (IVIG) and plasma exchanges (PE), with transient benefit. Eculizumab and efgartigimod were unsuccessful. Six years after onset he developed MC, with bulbar sign and respiratory distress, requiring NIV for 22 days. Courses of PE and IVIG were attempted. Due to neurological worsening, zilucoplan 32,4 mg/day was given. In the following 6 days we observed clinical improvement, leading to weaning from NIV. Zilucoplan was maintained and added to mychophenolate (2 g/day) and oral steroids, tapered over two months to 25 mg/day.

Our patient presented MC during the course of refractory MG. Zilucoplan exhibited rapid efficacy and good tolerability. Howard demonstrated long-term efficacy and safety in refractory MG. Maruani and Ito proposed zilucoplan as an efficacious therapeutic strategy in MC without adverse effects. Interestingly, Maruani cases showed worsening of myasthenic symptoms after zilucoplan discontinuation. The reported cases support the hypothesis that zilucoplan is a valid therapeutic option in MG and may be a potential rescue therapy in MC.

THURSDAY, MAY 14TH, 2026

**POSTER SESSION MYOPATHIES |
odd numbers**

15:00-16:30

Chairs: Angela Berardinelli, Gaia Scarpini

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P005 - Cod. 143307

AN ITALIAN SINGLE-CENTER LONGITUDINAL STUDY OF RESPIRATORY PROGRESSION IN FSHD1 OVER 20 YEARS

Vercelli L.^{*1}, Gadaleta G.¹, Urbano G.¹, Rolle E.¹, Leopizzi E.¹, Boschi S.¹, Ribolla F.², Solidoro P.², Mongini T.¹

¹ Neuromuscular Unit, Department of Neurosciences "Rita Levi Montalcini", University of Turin, Turin, Italy, ² Division of Respiratory Diseases, Cardiovascular and Thoracic Department, Città della Salute e della Scienza, University of Turin, Turin, Italy

Respiratory dysfunction is a recognized but still underexplored component of facioscapulohumeral muscular dystrophy type 1 (FSHD1). While cross-sectional studies suggest variable degrees of respiratory involvement, data describing its long-term progression are limited, particularly over extended follow-up periods.

We performed a retrospective, single-center longitudinal study including 46 patients with genetically confirmed FSHD1, followed for up to 20 years. Respiratory and motor assessments were collected at baseline and approximately every five years thereafter. Respiratory outcomes included forced vital capacity (FVC), forced expiratory volume in one second (FEV₁), maximal inspiratory and expiratory pressure (MIP/MEP). Motor involvement was evaluated using the Medical Research Council (MRC) scale, FSHD clinical score, and Clinical Categories.

At baseline, mean age was 43.5±14.2 years and mean disease duration was 20.3±15.4 years; all patients were ambulatory. During follow-up, 37.0% of patients lost ambulation and 34.8% initiated nocturnal ventilatory support. FVC declined from a mean of 108.5% predicted at baseline to 91.6% after 20 years. Respiratory muscle strength showed a steeper reduction, with annual decreases of -0.78 cmH₂O for MIP and -1.54 cmH₂O for MEP (p < 0.001). Only CCEF FSHD score was independently associated with a faster decline in FVC and MEP.

FSHD1 is characterized by a slow but persistent deterioration of respiratory function, with expiratory muscle weakness being particularly pronounced. Clinically meaningful respiratory decline and the need for ventilatory support occur more frequently after loss of ambulation. These findings support the relevance of respiratory measures as potential primary outcomes in clinical trials targeting FSHD1.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P007 - Cod. 143517

BENT SPINE PHENOTYPE IN LATE ONSET FSHD: INSIGHTS FROM A RETROSPECTIVE MULTICENTER STUDY

Torri F.^{*1}, Bortolani S.², Torchia E.², Gadaleta G.⁴, Vercelli L.³, De Maria M.⁵, Zoppi D.⁵, Risi B.⁷, Straffella C.⁶, Colantoni L.⁶, Monforte M.², Ruggiero L.⁵, Siciliano G.¹, Giardina E.⁶, Mongini T.³, Filosto M.⁷, Ricci E.², Ricci G.¹

¹ Department of Clinical and Experimental Medicine, Pisa, Italy, ² Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma, Italy, ³ Neuromuscular Unit, Department of Neurosciences, University of Turin, Torino, Italy, ⁴ Neuromuscular Unit, Department of Neurosciences, Torino, Italy, ⁵ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Napoli, Italy, ⁶ Istituto Santa Lucia, Roma, Italy, ⁷ NeMO Center, Brescia, Italy

In facioscapulo-humeral dystrophy (FSHD) several genetic and epigenetic factors are taken into consideration to explain the extreme phenotypic variability encountered in this disease. A phenotype characterized by a predominant and/or precocious involvement of axial muscles compared to other more commonly affected muscular groups in FSHD is reported. These subjects are categorized as "atypical" (i.e. Category D) by the CCEF clinical tool.

In this study, we retrospectively collected baseline and follow-up clinical, genetic and paravertebral and lower limbs muscle MRI data from 29 patients categorized as D1 or D2 according to the CCEF clinical scale, presenting axial weakness in the form of bent spine syndrome. Subjects had a mean age at symptoms onset of 57,9 years. The D4Z4 allele size ranged from 16 to 41 kb, with a mean of 34 kb. A total of 24 subjects presented bent spine as an initial symptom, while 4 presented more classical FSHD phenotypes with later predominance of axial involvement. Muscle MRI data was available for 11 subjects. Most of the cases were sporadic.

Our data stress out the need to include FSHD in the diagnostic process for late

onset axial myopathy, as it represents a phenotypic subgroup associated to DRAs. This cohort presents a later age at disease onset compared to subjects with classical FSHD phenotypes and other D subjects' cohorts previously published, which included mixed phenotypes. The D4Z4 allele range is confirmed in the higher size spectrum in our cohort.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P009 - Cod. 143387

FRG2A IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY: LINKING NUCLEOLAR DYSFUNCTION WITH DIFFERENTIATION-DEPENDENT TRANSLATIONAL FAILURE

Salsi V.^{*1}, Losi F.¹, Perenthaler E.², Lauria F.², Manfredi M.³, Viero G.², Tupler R.¹

¹ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, ² Institute of Biophysics, CNR Unit, Trento, Italy, ³ Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy, Novara, Italy

Facioscapulohumeral muscular dystrophy (FSHD) is caused by contraction of the D4Z4 macrosatellite repeat at chromosome 4q35, leading to epigenetic deregulation of nearby loci. Among them, FRG2A is consistently overexpressed in FSHD muscle and functions as a heterochromatin-associated long non-coding RNA (lncRNA) within a multicopy paralog family, directly regulating ribosomal DNA transcription and global protein synthesis.

Using an integrated multi-omics approach, we investigated translational control during myogenic differentiation.

Chromatin and RNA analyses reveal nucleolar and ribosomal alterations associated with reduced pre-rRNA levels in FSHD cells. Quantitative mass spectrometry in FSHD myoblasts identifies decreased abundance of proteins involved in ribosome biogenesis, translation, and intracellular transport, together with increased expression of splicing-related factors. Despite these molecular alterations, polysome profiling shows that undifferentiated FSHD myoblasts largely preserve translational activity. In contrast, during differentiation into myotubes, FSHD cells display accumulation of 80S monosomes and reduced ribosome engagement, indicating impairment of translational efficiency.

Consistently, proteomic profiling of differentiated FSHD myotubes reveals underrepresentation of muscle-specific proteins involved in sarcomere organization and contraction, despite compensatory up-regulation of ribosomal proteins and rRNA processing factors. This suggests that FSHD cells attempt to restore ribosome output during differentiation, but this response remains ineffective.

We propose that FRG2A-associated nucleolar dysfunction establishes a latent ribosomal vulnerability that becomes critical during myogenic differentiation, leading to functionally altered ribosomes and selective failure in muscle protein synthesis.

Together, our findings identify differentiation-dependent translational failure as a central mechanism linking repeat-driven lncRNA deregulation to muscle wasting in FSHD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P011 - Cod. 143822

HUMANISTIC BURDEN OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY: EVIDENCE FROM A SYSTEMATIC LITERATURE REVIEW

Danosi C.^{*1}, Kinter E.¹, Emich H.², Beckerman R.²

¹ Avidity Biosciences, Inc., San Diego, United States of America, ² Mapple Health Group, New York, United States of America

Facioscapulohumeral muscular dystrophy (FSHD) is a rare, progressive neuromuscular disorder associated with muscle weakness,

functional impairment, and reduced quality of life (QoL). While clinical features of FSHD are increasingly described, broader humanistic burden experienced by patients is less well-characterized. This review synthesized evidence on health-related QoL (HRQoL), symptoms, and patient-reported outcomes (PROs) in individuals with FSHD.

This review synthesized evidence on health-related QoL (HRQoL), symptoms, and patient-reported outcomes (PROs) in individuals with FSHD. MEDLINE, Embase, and Cochrane databases were searched (inception–August 2025), as well as neuromuscular-/disease-relevant conference proceedings. Studies evaluating humanistic burden in FSHD were eligible. Observational studies, clinical trials, and qualitative studies were included. Outcomes were synthesized descriptively by domain.

89 studies reported assessments of humanistic burden in FSHD using > 90 unique instruments. General HRQoL was the most frequently assessed ($n = 37$), followed by fatigue ($n = 26$), pain ($n = 20$), disease-specific QoL ($n = 18$), and disability/function ($n = 9$). Physical versus mental components of outcome instruments were consistently more impaired. Fatigue and pain were highly prevalent, with many patients reporting symptoms interfering with daily activities/participation. Disease-specific measures highlighted substantial impacts related to muscle weakness, reduced independence, and activity limitations. Qualitative studies ($n = 16$) underscored psychosocial consequences, including challenges related to facial weakness, social interactions, uncertainty about disease progression, and concerns about future loss of independence.

FSHD is associated with substantial, multidimensional humanistic burden affecting physical, functional, and psychosocial domains. The heterogeneity of PRO instruments used in FSHD highlights lack of consensus on optimal measurements. Unmet needs exist for a more standardized approach and appreciation of clinical meaningfulness to capture patient experience and support patient-centered evaluation of emerging therapies.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P013 - Cod. 143031

LONGITUDINAL CHARACTERIZATION OF ASYMPTOMATIC AND MINIMALLY AFFECTED FSHD PATIENTS

Bortolani S.^{*1}, Di Marco C.², Torchia E.², Ravera B.², Marchese D.², Strafella C.⁴, Megalizzi D.⁴, Colantoni L.⁴, Giardina E.⁴, Tasca G.³, Ricci E.¹, Monforte M.¹

¹ UOC di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, ² Università Cattolica del Sacro Cuore, Roma, Italy, ³ John Walton Muscular Dystrophy Research Centre, NIHR Newcastle Biomedical Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, ⁴ UOC di Diagnostica di Laboratorio e Medicina Genomica Fondazione Santa Lucia IRCCS, Roma, Italy

To facilitate the development and approval of targeted therapies for Facioscapulohumeral muscular dystrophy (FSHD), a better understanding of the molecular mechanisms underlying its marked phe-

notypic variability is essential. Non-penetrant gene carriers (NPGCs) represent a unique subgroup within the FSHD population. The mechanisms accounting for the absence of disease expression in these individuals remain poorly understood.

This study aimed to characterize a cohort of asymptomatic or minimally affected FSHD carriers using clinical evaluation and muscle MRI, and to longitudinally assess signs of disease activity and progression. We retrospectively enrolled NPGCs and minimally affected FSHD patients (isolated facial involvement) aged > 20 years at last follow-up, with available upper and lower limb muscle MRI. Demographic, epigenetic, and radiological data were collected and analyzed in relation to disease penetrance and progression.

Among 543 FSHD patients followed at our center, a retrospective cohort of over 60 NPGCs and minimally affected individuals (mean age 40 ± 13 years; 77% female) was identified. More than 1/3 had at least one fatty replaced muscle at baseline MRI. The follow-up period ranged from 1 to 14 years; no patients showed clinical progression, while approximately one quarter of MRI examinations revealed slight progression in fatty-replacement scores.

These preliminary findings highlight the value of muscle MRI in detecting muscle involvement and disease progression not captured by clinical assessment alone, especially in NPGCs and minimally affected patients. Extending longitudinal follow-up and expanding the cohort in a multicentre effort will be crucial to further explore genetic and epigenetic modifiers of disease penetrance and progression in FSHD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P015 - Cod. 143491

LOWER LIMB MUSCLE FAT-FRACTION LONGITUDINAL CHANGE IN PATIENTS AFFECTED BY FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY: A SYSTEMATIC REVIEW OF QUANTITATIVE MRI STUDIES

Marchese D.^{*1}, Bortolani S.², Torchia E.¹, Ravera B.¹, Di Marco C.¹, Ricci E.², Monforte M.²

¹ Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ² Unità Operativa Complessa di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive and heterogeneous muscular dystrophy, presenting challenges for disease monitoring and clinical trial outcome selection.

Quantitative muscle magnetic resonance imaging (qMRI), particularly fat fraction (FF) quantification, has emerged as an objective biomarker for assessing muscle involvement and disease progression.

The aim is to systematically review the evidence on the use of quantitative MRI for longitudinal assessment of muscle involvement in patients with FSHD.

This review was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA). We searched for articles written in English in PUBMED. The last search was performed on February 3rd, 2025, but the work is still in progress to

extend the research to other potential sources of relevant evidence. Selection criteria for inclusion comprised longitudinal studies employing qMRI to quantify muscle FF in FSHD patients. Extracted data included cohort size, follow-up duration, MRI protocol used, annual FF change, baseline disease severity, inflammatory MRI features and correlations with functional outcomes.

Ten studies have been identified so far for qualitative synthesis following full-texts screening. The cohorts of patients studied ranged from 9 to 163 individuals (total of 362 patients), with follow-up periods between 1 and 5 years. The mean annual FF increase in the different studies ranged from 1.3% to 5.4% per year. Data analysis is undergoing and results will be presented at the conference.

The results of our study could be potentially leveraged as a reference point for the comparison of fat fraction change in interventional clinical trial.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P017 - Cod. 143492

METABOLOMICS REVEALS MULTIPLE METABOLIC ALTERATIONS AND BIOMARKERS OF DISEASE SEVERITY IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Reynier P.¹, Michel M.¹, Vandeputte P.², Nuredini A.*³, Zoppi D.⁴, Gillet C.², Albano N.³, Pini S.³, De Maria M.⁴, Blanchet O.⁵, Gueguen N.¹, Chao De La Barca J.¹, Ruggiero L.⁴, Tupler R.³, Spinazzi M.²

¹ Department of Biochemistry and Molecular Biology, University Hospital of Angers, Angers, France, ² Neuromuscular Reference Center, Department of Neurology, University Hospital of Angers, Angers, France, ³ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, ⁴ Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples "Federico II", Napoli, Italy, ⁵ Biobank of the University Hospital of Angers, Angers, France

Facioscapulohumeral muscular dystrophy is one of the most common adult-onset myopathies and is causally associated with a contraction of the D4Z4 macrosatellite repeat array on chromosome 4. It presents with a variable pattern of progressive muscle weakness affecting the face, shoulder girdle, and lower limbs. The pathophysiological mechanisms underlying the disease remain incompletely understood and no effective treatments are currently available. Moreover, the lack of validated biomarkers limits the assessment of disease progression and therapeutic effects in clinical trials. Metabolic dysfunction has been hypothesized as a contributing factor, yet this hypothesis has been explored only in a limited number of studies. In this multicenter, observational, cross-sectional case-control study, we conducted quantitative plasma metabolomics using mass spectrometry in 57 patients with mild to moderate facioscapulohumeral muscular dystrophy, alongside with 63 age- and sex-matched controls. We analyzed the data by an integrative approach combining univariate and multivariate analyses to discriminate metabolomes of patients from controls.

We identified 57 discriminant metabolites that distinguish patients from controls and indicate dysregulation of several metabolic pathways.

These findings highlight substantial systemic metabolic disturbances in the early stages of facioscapulohumeral muscular dystrophy, offering new avenues for therapeutic interventions biomarkers identification.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P019 - Cod. 143058

PROFILING FSHD PHENOTYPES BY COMBINING MUSCLE MRI AND GAIT ANALYSIS: AN INTEGRATIVE APPROACH

Torchia E.*¹, Rocca F.², Denza G.², Pelliccioni M.³, Bortolani S.³, Trombetta V.³, De Angelis S.⁴, Ravera B.¹, Di Marco C.¹, Marchese D.¹, Monforte M.³, Tasca G.⁶, Vannozzi G.⁵, Rosellini G.⁴, Ricci E.³

¹ Neuroscience Department, Università Cattolica del Sacro Cuore, Rome, Italy, ² ITOP SpA Officine Ortopediche, Palestrina, Italy, ³ UOC di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ⁴ Department of Clinical Sciences and Translational Medicine – Orthopedic Techniques, University of Rome "Tor Vergata", Rome, Italy, ⁵ Department of Movement, Human and Health Sciences, University of Rome "Foro Italico", Rome, Italy, ⁶ John Walton Muscular Dystrophy Research Centre, NIHR Newcastle Biomedical Research Centre Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom

Facioscapulohumeral muscular dystrophy (FSHD) is characterized by a markedly heterogeneous muscle involvement, often including axial muscles, with different consequences on function and ambulation.

The aim of this study was to apply an integrated clinical-imaging-gait analysis approach to characterize distinct phenotype in FSHD. Genetically confirmed FSHD patients with lower-limb involvement and unaided ambulation were included. Muscle-MRI was used to stratify patients into radiologically defined (RD) groups. Kinematic-gait parameters were compared across groups to identify phenotype-specific patterns.

Thirty-four patients (53% male; mean age 54.9±11.6 years) were enrolled. RD group 1 included patients with predominant axial involvement (56%, 19/34) and was subdivided into an "atypical axial" phenotype with selective paraspinal involvement (sub-group 1.1) and an "advanced axial" phenotype with combined and severe trunk and lower-limb involvement (sub-group 1.2). Three patients (from sub-group 1.1) showed a camptocormic phenotype. The remaining patients displayed a backward trunk displacement with pelvic anteversion ("sacral-sitting" sign). Gait analysis revealed distinct compensatory strategies: sub-group 1.1 showed increased knee extension during heel-strike, whereas sub-group 1.2 exhibited increased knee flexion during the swing-phase. RD group 2 (44%, 15/34) included patients with predominant lower-limb involvement and comprised a "pure-distal" phenotype (sub-group 2.1) and a "femoro-distal" phenotype (sub-group 2.2). Patients in sub-group 2.2 showed increased knee extension during mid-stance compared to sub-group 2.1, in

severe cases leading to clinical recurvatum.

An integrated MRI-gait analysis approach identifies distinct phenotypes with specific radiological-functional features. This strategy improves the characterization of axial involvement and supports MRI-driven stratification as a meaningful tool in FSHD.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY (FSHD)

Abstract P021 - Cod. 143028

SHORT-TERM EFFECTS OF A STRUCTURED HIGH-INTENSITY TRAINING REHABILITATION PROGRAM IN FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY: A PROSPECTIVE OBSERVATIONAL STUDY

Larentis A.*, Zuccarino R., Barp A., Ferrari V., Masé Gallizioli C., Stano S., Mercuriali B., Foschi L., Corradi E.
Centro Clinico NeMO, Trento, Italy

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive neuromuscular disorder characterized by muscle weakness, pain, fatigue and functional limitations. Exercise-based rehabilitation is recommended, but evidence regarding the clinical impact and safety of structured high-intensity rehabilitation programs in FSHD remains limited.

To evaluate the short-term clinical effects and safety of a 3-week structured High Intensity Training (HIT) rehabilitation program in patients with FSHD. The intervention consisted of a supervised, multimodal program delivered 5 days per week, including individualized strength and resistance exercises, balance and motor control training, and daily high-intensity aerobic exercise with monitored workloads.

Twelve patients with genetically confirmed FSHD completed the program with high adherence. Muscle strength improved bilaterally after the intervention. Functional outcomes improved, with reductions in both FSHD Clinical Score and FSHD Composite Outcome Measure. Walking capacity increased at the 6-Minute Walking Test. Pain markedly decreased, along with reduced perceived fatigue. Patient-reported outcomes (FSHD-HI) indicated a reduction in perceived disease burden. No clinically relevant increases in creatine kinase or myoglobin were observed.

A short-term, structured high-intensity, multimodal rehabilitation program appears to be safe and associated with clinically meaningful improvements in muscle strength, functional performance, pain and patient-reported health status in patients with FSHD. Follow-up assessments at 12 weeks are ongoing and will be presented to evaluate the sustainability of treatment effects.

GENETIC (MYOPATHIES)

Abstract P023 - Cod. 143261

FROM EXOME TO DISEASE: A NOVEL CANDIDATE GENE FOR GLYCOGEN STORAGE

DISEASE DUE TO MUSCLE PHOSPHORYLASE KINASE DEFICIENCY

Vicidomini G.*¹, Di Letto P.², Scarpato M.¹, Palmieri F.P.¹, Bonolis V.², Esposito G.³, Scutifero M.³, Picillo E.³, Ruggiero L.⁴, Zoppi D.⁴, Santorelli F.M.⁵, Doccini S.⁵, Piluso G.¹, Torella A.¹, Nigro V.¹

¹ Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy, ² Telethon Institute of Genetics and Medicine, Pozzuoli, Naples, Italy, ³ Azienda Ospedaliera Universitaria "Luigi Vanvitelli", Naples, Italy, ⁴ Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples "Federico II", Naples, Italy, ⁵ Molecular Medicine for Neurodegenerative and Neuromuscular Diseases Unit, IRCCS Stella Maris Foundation, Pisa, Italy

Muscle-specific deficiency of phosphorylase kinase (PhK) causes glycogen storage disease (GSD) with adolescence or adulthood onset. It is clinically connoted by exercise intolerance with early fatigability, myalgia, cramps, and sometimes myoglobinuria. Symptoms are usually mild, and myopathy may be asymptomatic. To date, pathogenic variants have been only identified in the muscle isoform of the PhK subunit alpha encoded by the PHKA1 gene.

Our aim is to investigate the molecular basis of GSD due to low muscle PhK activity, exploring all the genes encoding its subunits.

Here we present the case of a 20-year-old man born to unrelated, healthy parents. On clinical examination he presented mild muscular weakness, episodic rhabdomyolysis with elevated creatine kinase and myoglobinuria after intense exercise. Trio-based exome sequencing detected two compound heterozygous variants in the PhK catalytic subunit gamma gene PHKG1, NM_006213.5:c.697C > G;p.Arg-233Gly and c.1003C > T;p.Arg335* inherited from the father and the mother, respectively. Even though they are classified as VUS according to ACMG criteria, their damaging effect is strongly predicted by several in-silico tools, and assessed by the functional studies we practiced on muscle biopsy. The biochemical assay displayed an absolute reduction in enzyme activity, and a mild myopathic damage was shown at optical microscopy. All these findings, together with the absence of any other noteworthy variant, suggests that PHKG1 could be the causative gene.

Overall, these data build the underpinnings to define PHKG1 as novel disease-causing gene associated with GSD due to muscle PhK deficiency. Further evidence is necessary to deepen the molecular understanding of this condition.

GENETIC (MYOPATHIES)

Abstract P025 - Cod. 143017

INTEGRATED ELECTROPHYSIOLOGICAL, CELLULAR, AND PHARMACOLOGICAL PROFILING REVEALS VARIANT-SPECIFIC MECHANISMS IN SCN4A-RELATED MYOTONIA

Meola G.*¹, Frosio A.², Calamaio S.³, Pagliarani S.⁴, Cirillo F.⁵, Melgari D.², Prevostini R.³, Lo Presti F.², Lucchiari S.⁶, Magri F.⁴, Corti S.⁶, Comi G.⁶, Anastasia L.⁵, Pappone C.⁵, Rivolta I.³

¹ Department of Neurorehabilitation Sciences, Casa di Cura Igea, Milan, Italy, ² ilano, Italy, ³ Institute of Molecular and Translational Cardiology, IRCCS Policlinico San Donato, San Donato Milanese, Italy, ⁴ School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy,

⁴ Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy, ⁵ Faculty of Medicine and Surgery, Vita-Salute San Raffaele University, Milano, Italy, ⁶ Neuroscience Section, Dino Ferrari Centre, Department of Pathophysiology and Transplantation, University of Milan, Milano, Italy

Non-dystrophic myotonias are rare skeletal muscle channelopathies characterized by delayed muscle relaxation and clinical stiffness. Myotonia congenita is caused by pathogenic variants in the CLCN1 gene, encoding for the skeletal muscle chloride channel (ClC-1), and can be inherited in both dominant and recessive modes. Paramyotonia congenita and sodium channel myotonia are dominant inherited and are caused by mutations in SCN4A gene that encodes for the skeletal muscle sodium channel (Nav1.4).

We present three cases of myotonic patients carrying both a missense variant in the SCN4A gene and the known variant G190S in the CLCN1 gene. G190S is frequently found in Italian myotonic patients and has been described as a cause of myotonia when inherited in both dominant and recessive ways.

The molecular mechanisms underlying the three missense variants p.K1308R, p.R1451H, and p.M1701V were investigated using an integrated approach combining electrophysiology, protein trafficking assessment, and evaluation of endoplasmic reticulum stress. Each variant revealed a distinct pathogenic signature: p.K1308R and p.M1701V primarily altered channel gating, whereas p.R1451H exhibited profound cellular impairment, including intracellular retention, reduced membrane expression, and robust activation of endoplasmic reticulum-stress pathways. Functionally, p.K1308R and p.R1451H caused marked reductions in current density and slowed activation kinetics, while p.M1701V produced milder perturbations. Mexiletine modulates gating abnormalities in a variant-specific manner, strengthening the clinical relevance of mexiletine as a first-line drug. Overall, the findings showed that clinically similar myotonic phenotypes may arise from divergent molecular defects and emphasize the relevance of precision medicine approaches tailored to variant-specific pathogenic mechanisms.

GENETIC (MYOPATHIES)

Abstract P027 - Cod. 143327

LATE-ONSET IDIOPATHIC AXIAL MYOPATHY: INSIGHTS FROM THE PADOVA COHORT

Capece G.^{*1}, Di Feo M.F.², Sogus E.³, Petrosino A.³, Fornasier T.³, Vianello S.³, Bertolin C.⁴, Gorgoglione D.³, Sabbatini D.³, Sorarù G.³, Minicuci G.M.⁴, Bello L.³, Udd B.⁵, Savarese M.², Pegoraro E.³
¹ PhD Program in Translation Specialistic Medicine "G.B. Morgagni", Curriculum "Clinical and Translational Neurosciences, University of Padova, Padova, Italy, ² Folkhälsan Research Center, Helsinki, Finland, ³ Department of Neurosciences, DNS, University of Padova, Padova, Italy, ⁴ Padova University Hospital, Padova, Italy, ⁵ Tampere University Hospital, Tampere Neuromuscular Center, Tampere, Finland

Axial myopathies are characterized by predominant involvement of paraspinal muscles, causing camptocormia (CC) and dropped head (DH). The differential diagnosis includes genetic and acquired myopathies; however, many patients remain without a definite molecular

diagnosis. Idiopathic axial myopathy is a rare late-onset condition with unexplored molecular bases.

We aim to provide a clinical and molecular characterization of a single-center cohort. We retrospectively selected patients with idiopathic axial myopathy, evaluated at the Neuromuscular Unit of Padova between 2017 and 2025. Diagnostic workup included clinical evaluation, muscle biopsy, and next-generation sequencing.

Thirty-one patients (25 females - 6 males) were identified (mean age at onset 65.6 ± 7.6 years). Neurological examination showed CC in 21 patients, DH in 7 and both CC+DH in 3. Muscle biopsy (limb muscles) showed in all mild myopathic changes without structural muscle fibers abnormalities. NGS results were available for 12 patients. No causative gene has been identified. However, heterozygous TTN truncating variants (TTNtv) were identified in four patients (2 nonsense, 1 frameshift, 1 splicing): three are ultra-rare, and one absent in gnomAD; all involve exons expressed in skeletal muscle.

Idiopathic axial myopathy is a late-onset condition, more common in females, typically presenting with camptocormia. Muscle biopsy in non-axial muscles plays a supportive role in diagnosis. Our preliminary genetic findings are consistent with a recent report (DiFeo 2026, Eur J Neurol), showing a significant increased prevalence of heterozygous TTNtv in this condition compared with general population (16% vs ~1%). As a result, heterozygous TTNtv variants may contribute to disease pathogenesis.

GENETIC (MYOPATHIES)

Abstract P029 - Cod. 143283

NOVEL ZEBRAFISH KNOCK-IN MIMICS BOVINE PSEUDOMYOTONIA: A NEW ANIMAL MODEL FOR HUMAN BRODY MYOPATHY

Erba M.^{*1}, Akyurek A.E.¹, Dalla Barba F.², Sacchetto R.¹

¹ Dipartimento di Biomedicina Comparata ed Animale, Padova, Italy,

² Dipartimento di Scienze Biomediche, università di Padova, Padova, Italy

Brody myopathy (BM) is an ultra-rare autosomal recessive skeletal muscle disorder caused by mutations in ATP2A1, encoding Sarco(Endo)plasmic Reticulum Ca^{2+} -ATPase isoform 1 (SERCA1). SERCA1 drives sarcoplasmic reticulum Ca^{2+} reuptake, which is essential for muscle relaxation. BM missense mutations trigger SERCA1 misfolding and instability, reducing pump availability without necessarily abolishing its activity. Lack of small-animal models has limited functional and therapeutic studies.

For this reason, we decided to generate and characterize a zebrafish knock-in model of the SERCA1 R164H mutation to investigate intracellular Ca^{2+} handling in BM and to establish a platform for testing small molecule correctors targeting SERCA1 misfolding.

Bovine congenital pseudomyotonia (PMT), the only established BM counterpart in mammals, stems from SERCA1 R164H mutations. We generated a CRISPR/Cas9 knock-in zebrafish (Danio rerio) line harboring the orthologous atp2a1 R164H for in vivo analyses and drug screening.

Homozygous mutants were viable, fertile, with normal development and preserved skeletal muscle morphology. Basal locomotor activity matched wild-type siblings, but functional deficits emerged under

stress. Adult mutants showed reduced SERCA1 protein levels, mirroring bovine PMT and human BM.

This subtle-phenotype model enables intracellular Ca^{2+} imaging with reporters to explore handling and compensatory mechanisms. It provides a platform to test small molecules targeting misfolding, including CFTR correctors from cystic fibrosis, aiming to restore SERCA1 stability and function.

GENETIC (MYOPATHIES)

Abstract P031 - Cod. 143034

ONE EXON, MULTIPLE PHENOTYPES: RECESSIVE TITINOPATHIES ASSOCIATED WITH VARIANTS IN THE LAST TTN EXON (364)

Di Feo M.F.¹, Rees M.², Lillback V.¹, Capece G.³, Perrin A.⁴, Kho A.L.², Tard C.⁵, Biancalana V.⁶, Laporte J.⁷, Fradin M.⁸, Cossée M.⁹, Duffy C.¹⁰, Kornblum C.¹¹, Bartolomaeus T.¹², Kleefeld F.D.¹³, Nadaj Pakleza A.¹⁴, Salort Campana E.¹⁵, Esselin F.¹⁶, Walther-Louvier U.¹⁷, De Ridder W.¹⁸, Baets J.¹⁸, De Jonghe P.¹⁸, Mozaffar T.¹⁹, Spinazzi M.²⁰, Kopcilova J.²¹, Zidkova J.²¹, Roggenbuck J.²², Murtazina A.²³, Kuchina A.²³, Kurbatov S.²⁴, Schagina O.²⁵, Chausova P.²³, Subbotin D.²³, Marakhonov A.²³, Jungbluth H.²⁶, Petrucci A.²⁸, Hackman P.¹, Sarpuranta J.¹, Udd B.²⁷, Gautel M.², Savarese M.¹

¹ Folkhälsan Research Center, Helsinki, Finland, ² Randall Centre for Cell & Molecular Biophysics, School of Basic & Medical Biosciences, King's College, London, United Kingdom, ³ PhD Program in Translation Specialistic Medicine "G.B. Morgagni", Curriculum "Clinical and Translational Neurosciences, University of Padova, Italy, Padova, Italy, ⁴ Centre Hospitalier Universitaire de Montpellier, Montpellier, France, ⁵ North-East Ile-de-France Neuromuscular Pathology Reference Center, University Hospital Center of Lille, Lille, France, ⁶ Laboratory of Genetic Diagnosis, Faculty of Medicine, CHRU, Strasbourg, Strasbourg, France, ⁷ IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire), Inserm U1258, CNRS UMR7104, Université de Strasbourg, Strasbourg, France, ⁸ Service de Génétique Clinique, Centre Hospitalier Universitaire de Rennes, Rennes, Rennes, France, ⁹ Laboratoire de Génétique Moléculaire, Centre Hospitalier Universitaire de Montpellier, Montpellier, France, ¹⁰ Department of Neurooncology, Center for Neurology and Integrated Oncology (CIO), University Hospital Bonn, Bonn, Germany, ¹¹ Department of Neuromuscular Diseases, Center for Neurology, University Hospital Bonn, Bonn, Germany, ¹² Institute of Human Genetics, University of Leipzig Medical Center, Leipzig, Leipzig, Germany, ¹³ Department of Neurology, Berlin Institute of Health (BIH), Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt, Universität zu Berlin, Berlin, Germany, ¹⁴ Centre de Référence des Maladies Neuromusculaires NEIdF and ERN EURO-NMD, Neurology Department, University Hospital of Strasbourg, Strasbourg, France, ¹⁵ Referral Centre for Neuromuscular Diseases and ALS, La Timone University Hospital, Aix-Marseille University, Marseille, Marseille, France, ¹⁶ Department of Neurology, French Greater South West Reference Center for Neuromuscular Diseases, Hôpital Gui de Chauliac, University Hospital Center Montpellier, Montpellier, France, ¹⁷ Department of Pediatric Neurology, French Greater South West Reference Center for Neuromuscular Diseases, Hôpital Gui de Chauliac, University Hospital Center Montpellier, Montpellier, France, ¹⁸ Department of Neurology, Neuromuscular Reference Centre, Antwerp University Hospital, Antwerp, Belgium; Translational Neurosciences and Peripheral Neuropathy Group,

University of Antwerp, Antwerp, Belgium; Laboratory of Neuromuscular Pathology, Institute, ¹⁹ Department of Neurology, University of California Irvine, California, USA, Irvine, United States of America, ²⁰ Neurology Department, CHU d'Angers, France; Institute of Neurobiology and Neuropathology CHU d'Angers, France; Neuromuscular Reference Center, Department of Neurology, CHU d'Angers, France; MITOLAB, INSERM U1083, France, Angers, France, ²¹ Centre of Molecular Biology and Genetics, Brno University Hospital, Brno, Czech Republic, ²² Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, USA, Columbus, United States of America, ²³ Research Centre for Medical Genetics, Moscow, Russian Federation, ²⁴ Voronezh NN Burdenko State Medical University, Voronezh, Russian Federation, ²⁵ DNA-Diagnostics Laboratory, Research Centre for Medical Genetics, Moscow, Russian Federation, ²⁶ Department of Paediatric Neurology, Neuromuscular Service, Evelina London Children's Hospital, Guy's and St Thomas' Hospital NHS Foundation Trust, London, United Kingdom, ²⁷ Neuromuscular Research Center, Tampere University and University Hospital, Tampere, Finland, ²⁸ Azienda Ospedaliera San Camillo-Forlanini, Roma, Italy

Pathogenic variants in the last exon (exon 364) of the TTN gene were the first identified cause of skeletal muscle titinopathies. Pathogenic variants in the last exon cause dominant tibial muscular dystrophy in heterozygosity, whereas biallelic variants lead to clinically heterogeneous recessive phenotypes. Next-generation sequencing has further expanded this spectrum, complicating variant interpretation. To define the clinical and genetic spectrum of recessive titinopathies involving exon 364 and to refine pathogenicity assessment

We investigated 18 patients from international centers carrying at least one TTN exon 364 variant in homozygosity or in compound heterozygosity with a second pathogenic TTN variant. Twelve distinct exon 364 variants were identified, including four previously unreported. One patient carries an out-of-frame Alu element insertion on the second allele, confirmed by long-read whole-genome sequencing. Clinical presentations ranged from severe childhood-onset myopathy to late-onset adult disease, and homozygous missense variants were associated with particularly severe phenotypes. Ten of eighteen patients showed widespread upper and lower limb muscle involvement, occasionally affecting finger flexors and pelvic girdle; one third exhibited paravertebral muscle involvement. Biophysical and cellular assays of previously untested missense variants demonstrated destabilization and misfolding of the M10 domain (the last immunoglobulin-like domain), therefore providing evidence supporting ACMG pathogenicity classification. Truncating variants in exon 364 were associated with disease only in homozygous or compound heterozygous states, while heterozygous carriers in the families were clinically unaffected

Variants in TTN exon 364 underlie a broad phenotypic spectrum of recessive titinopathies. Accurate interpretation requires integration of clinical findings, functional studies, and genomic analysis

GENETIC (MYOPATHIES)

Abstract P033 - Cod. 142888

PATIENT-DERIVED MYOTUBES AS A MODEL TO STUDY ION CHANNEL INVOLVEMENT IN MYOTONIA OBSERVED IN PLIN4-RELATED

MYOPATHY

Laghetti P.^{*1}, Altamura C.¹, Saltarella I.¹, Moroni I.², Ruggieri A.³, Gibertini S.³, Maggi L.³, Desaphy J.¹

¹ Section of Pharmacology, Department of Precision and Regenerative Medicine and Ionian Area, School of Medicine, University of Bari "Aldo Moro", Bari, Italy, ² Department of Pediatric Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ³ Neuroimmunology and Neuromuscular Disease Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy

PLIN4-related myopathy is a rare vacuolar myopathy caused by an expansion of a 33-amino acid motif in the amphipathic helix of Perilipin 4 (PLIN4). This defect results in abnormal protein accumulation beneath the sarcolemma, defective autophagy and formation of vacuoles, impairing skeletal muscle architecture and contractility. Clinically, the disease manifests with distal muscle weakness, while myotonia has been described in a subset of patients. Myotonic phenotypes are usually linked to pathogenic variants in the ion channel genes CLCN1 and SCN4A.

The aim of this study is to develop an in vitro model of PLIN4-related myopathy suitable for studying ion channel expression and their potential involvement in myotonia observed in these patients.

Immortalized myoblasts from an Italian family affected by PLIN4-related myopathy were differentiated into myotubes using transgene-free methods and gene expression was assessed by SYBR Green quantitative PCR. During differentiation, we observed a time-dependent upregulation of embryonic, neonatal, and adult myosin heavy chain isoforms, indicating progressive maturation of myotubes. The expression of CLCN1 and SCN4A increased after 14 and 21 days of differentiation compared to undifferentiated myoblasts.

These data show that myoblasts derived from patients with PLIN4-related myopathy underwent effective myogenic differentiation in vitro, with preserved expression of key ion channels involved in muscle excitability. Therefore, patient-derived myotubes represent a relevant in vitro model to investigate ion channel dysfunction and myotonia in PLIN4-related myopathy.

This work was funded by the Italian Ministry of Health and the European Union (Project code: PNRR-MR1-2023-12377360).

GENETIC (MYOPATHIES)

Abstract P035 - Cod. 143060

PROTEOMIC PROFILING REVEALS ALTERED LIPID METABOLISM AND FERROPTOSIS IN PLIN4-RELATED MYOPATHY

Testa S.^{*1}, Carnazzi A.¹, Salvi E.², Tomé S.³, Roos A.⁵, Hentschel A.⁴, Iannibelli E.¹, Nicolini De Gaetano L.¹, Gibertini S.¹, Maggi L.¹, Ruggieri A.¹

¹ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Data Science Center and Computational multi-Omics of Neurological Disorders (MIND) Lab – Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³ Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milano, Italy, ⁴ Leibniz-Institut für Analytische Wissenschaften – ISAS – e.V., 44139 Dortmund, Germany, ⁵ Pediatric Neurology, Faculty of Medicine, University

Children's Hospital, University of Duisburg-Essen, Essen, Germany, Essen, Germany

PLIN4-related myopathy is a rare autosomal dominant disorder caused by structural variations in exon 5 of PLIN4 (99-nucleotide repeat expansions or a 14-block duplication) that result in protein enlargement. Affected muscle fibers display subsarcolemmal and rimmed vacuolar accumulation of perilipin 4, which co-localizes with the autophagic markers p62/SQSTM1 and NBR1. This aberrant deposition drives progressive distal muscle weakness and the proportion of PLIN4-positive fibers correlates with disease severity.

We aimed to identify proteomic features associated with disease severity and uncover pathogenic pathways that may distinguish this disorder from other aggregate myopathies.

We performed label-free LC-MS proteomic profiling on whole-protein extracts from muscle biopsies (9 patients, 3 controls).

Principal component analysis separated patients from controls and revealed two distinct subgroups within the cohort, characterized by different levels of perilipin 4 deposition in muscle fibers, correlating with disease severity. Differential abundance and pathway enrichment analyses demonstrated dysregulation of energy metabolism and widespread alterations in protein homeostasis in patients.

The two patient subgroups were analysed separately and compared with controls and with each other using a three-group Kruskal-Wallis and Dunn's post hoc test. Pathway and Gene Ontology over-representation analysis was performed on the most differentially expressed proteins. When comparing controls with the most severely affected patients, fatty acid β -oxidation and oxidative stress pathways were upregulated. Moreover, ferroptosis and peroxisomal pathways were over-represented in the latter compared to the milder affected subgroup.

In summary, this unbiased label-free proteomic study identified major dysregulated pathways that provide insight into the pathobiology of PLIN4-related myopathy.

GENETIC (MYOPATHIES)

Abstract P037 - Cod. 143458

RHABDOMYOLYSIS AFTER VERTEBRAL SURGERY IN A YOUNG WOMAN WITH A HETEROZYGOUS TRUNCATING CASQ1 VARIANT

Cerfeda S.^{*1}, Capece G.¹, Sogus E.¹, Petrosino A.¹, Fornasier T.¹, Ferrero V.¹, Vianello S.¹, Papa V.², Bertolin C.³, Salviati L.³, Pegoraro E.¹, Bello L.¹

¹ Dipartimento di Neuroscienze DNS, Università degli Studi di Padova, Padova, Italy, ² UOC Anatomia ed Istologia Patologica, IRCCS Policlinico Sant'Orsola Malpighi, Bologna, Italy, ³ Unità di Genetica Medica, Dipartimento di Salute della Donna e del Bambino, Università degli Studi di Padova, Padova, Italy

We describe the case of a 33-year-old woman. Family history was relevant for scoliosis in her mother, without hyperCKemia or muscle weakness. The patient had a normal psychomotor development, and was diagnosed with scoliosis at the age of 8. At the age of 14, she underwent T4-L1 arthrodesis at a local Hospital, complicated by

post-operative rhabdomyolysis with severe weakness in the lower limbs and acute renal insufficiency (CK levels not available). She was subsequently (age 16) referred to our Center. Since then, we observed a stabilized clinical course with weakness localized in the posterior compartments of thighs and legs. Examination at 33 years showed difficulty walking on tiptoes, running, and hopping, positive Gowers sign, ischiocrural weakness; no sensory disturbances, normal deep tendon reflexes. CK varied between normal and mildly elevated (~400 U/L). EMG showed mixed myopathic and neurogenic alterations in lower limb muscles. A muscle biopsy (age 15, vastus lateralis) showed numerous atrophic type I fibers, with nuclear centralization and intense NADH positivity (SDH negative), and increase of pery- and endomysial connective tissue with fat deposition. Muscle MRI showed advanced fatty substitution in thigh muscles (posterior & anterior), gastrocnemii, and tibialis posterior. NGS revealed a heterozygous frameshift microdeletion in the CASQ1 gene: c.790delC, p.Leu264Ter. We hypothesize a causative role of calsequestrin haploinsufficiency in the rhabdomyolysis with permanent, non-progressive muscle damage. Segregation of the variant through trio WES, immunohistochemical analyses for triad proteins and ultrastructural studies on the muscle biopsy are underway.

GENETIC (MYOPATHIES)

Abstract P039 - Cod. 143281

RYR1 VARIANTS IN PATIENTS WITH ALTERNATIVE MOLECULAR DIAGNOSIS: A CASE SERIES

Magri F.^{*1}, Piga D.², Pagliarani S.², Velardo D.¹, Gagliardi D.², Abati E.², Del Bo R.³, Zanolini S.¹, Ripolone M.¹, Napoli L.¹, Ciscato P.¹, Moliterno N.¹, Alberti C.³, Lombardi M.⁴, Parisi M.², Sciacco M.¹, Corti S.³, Comi G.P.³, Ronchi D.³

¹ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular and Rare Disease Unit, Milano, Italy, ² IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy, ³ Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milano, Italy, ⁴ Neurology Unit, AOU Maggiore della Carità, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

RYR1 gene encodes the skeletal muscle ryanodine receptor (RyR1), the calcium release channel of the sarcoplasmic reticulum (SR). RYR1 variants are linked to neuromuscular disorders with onset from infancy to adulthood and a broad phenotypic and histopathological spectrum including susceptibility to malignant hyperthermia (MIM 145600) and congenital myopathy type 1A (MIM 117000), mainly with autosomal dominant inheritance, and autosomal recessive myopathy (Congenital myopathy type 1B, MIM 255320). The interpretation and functional validation of RYR1 defects is a challenge, further complicated by the high number of RYR1 variants identified in a diagnostic setting. RYR1 is also reported in the ACMG Recommendations for Reporting of Secondary Findings in clinical exome and genome sequencing. Next generation sequencing approaches, by targeting simultaneously multiple genes, allow the definition of a potential oligogenic basis of inherited disorders.

Here we present a case series of patients presenting heterogeneous neuromuscular disorders with established genetic diagnosis including polyglucosan body disease (GYG1, GBE1), congenital myopathy (FKRP), spinal and bulbar muscular atrophy (AR), dystrophinopathy (DMD).

In all of them we identified additional rare detrimental RYR1 molecular defects contributing to the cases presentation at clinical or subclinical (i.e. muscle histology) level.

We prompt to consider, even in patients with established molecular diagnosis, the analysis of RYR1 gene, although the contributing role of its variants can be masked by the underlining primary disease. The analysis and report of RYR1 variants can be relevant for genetic counseling and for a more accurate characterization of neuromuscular patients.

GENETIC (MYOPATHIES)

Abstract P041 - Cod. 143029

TPM2-RELATED MYOPATHIES: ENLARGING THE CLINICAL, GENETIC AND MYOPATHOLOGIC SPECTRUM

Cassandrini D.A.^{*1}, Das B.², Bevilacqua Rivas J.A.³, Homa T.⁴, Onnée M.², Rendu J.⁵, Malfatti E.⁶

¹ Immunology Unit, University Hospital, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, ² University Paris Est Créteil, Inserm, MUSKETHER LAB U955, IMRB, F-94010, Créteil, France, ³ Laboratorio de Patologia Muscular, Departamento de Neurologia y Neurocirugia, Clinica Davila, Santiago, Chile, ⁴ University of Skövde School of Health Sciences Div Biomedicine Box 408, 541 28, Skövde, Sweden, ⁵ Grenoble Institute of Neurosciences, Biochimie et Génétique Moléculaire, University Grenoble Alpes F-38000, Grenoble, France, ⁶ Reference Center for Neuromuscular Disorders, APHP Henri Mondor University Hospital, Créteil, France

The TPM2 gene encodes the skeletal isoform Tpm2.2 (β-tropomyosin). Mutations in this gene are primarily associated with rods and caps congenital myopathies (CMyo), arthrogryposis with hypercontractile phenotypes.

Here we describe four patients from three families showing strikingly different clinical and myopathologic features.

Patient 1 is a 65 yo woman with adult onset hand muscle weakness and thin muscle bulk and nemaline bodies in her muscle biopsy associated with a novel heterozygous TPM2 c.23T > C (p.Met8Thr) missense pathogenic variant. Patient 2 is a 76 yo man with an adult onset distal myopathy with prominent contracture, rods, central dense protein masses, desmin aggregates, and ring rods fibers, associated with a heterozygous deletion c.20_22del (p.Lys7)del pathogenic variant. Patient 3 and 4 are father and daughter showing early adult onset Achilles tendon contractures, myopathic features without rods (P3) linked to a novel missense TPM2 c.p.Asp20Gly pathogenic variant.

In conclusion, missense mutations in TPM2 selectively alter the regulation of contraction

by enhancing or weakening interactions with actin, thus reflecting the hyper- and hypocontractile phenotypes observed in patients. It is conceivable that TPM2 mutations alter both actin binding and troponin interaction, altering the regulation of muscle contraction. How-

ever, the mechanisms underlying the altered regulatory function of the mutations differ and depend on both the location and nature of the amino acid substitution. The resulting phenotypes are shaped by the combination of region-specific interactions between tropomyosin and its binding partners, defining the magnitude and degree of contraction, force production, and fatigue resistance.

MITOCHONDRIAL DISORDERS

Abstract P043 - Cod. 143375

BEYOND MYOPATHY: TWO CASES OF HEPATIC ONCOGENIC TRANSFORMATION IN ADULT DEOXYGUANOSINE KINASE DEFICIENCY.

Manzoni E.¹, Fanello S.², Caporali L.¹, Carelli V.¹, La Morgia C.^{*1}

¹ Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ² 3Medical Oncology, Comprehensive Cancer Centre, AUSL-IRCCS Reggio Emilia, Department/Unit Oncology Unit AUSL-IRCCS Reggio Emilia Italy, Reggio Emilia, Italy

Deoxyguanosine kinase deficiency (dGK) causes either severe early-onset hepatocerebral disease or adult-onset isolated myopathy. Hepatocellular carcinoma (HCC) is a rare complication of early-onset cases and is exceptional in the adult myopathic variant. This report stresses oncogenic risk and the need for regular surveillance.

We here describe two adult siblings (female Patient 1, male Patient 2), whose clinical data were already partially reported in 2018, with late-onset mitochondrial myopathy presenting in their 30s with progressive bilateral ptosis and proximal weakness. Muscle biopsy showed myopathic changes with COX-deficient and ragged-red fibers and mtDNA depletion. Both carried compound heterozygous pathogenic DGUOK variants (c.3A > G [p.M1I] and c.586C > T [p.P196S]) and presented multiple mtDNA deletions. Longitudinal follow-up revealed persistent mild hypertransaminasemia as the sole early hepatic abnormality. Hepatic nodules were later detected and

initial liver biopsies were non-malignant. After a prolonged stable phase new nodules emerged and a second biopsy confirmed HCC in both patients. Despite prompt oncologic management, unfortunately they both recently died at 72 and 68 years of age respectively.

We also reviewed PubMed (Jan 2001–May 2025) for HCC in dGK deficiency finding other four cases. HCC is rarely reported, predominantly in early-onset hepatocerebral phenotypes, with only one prior adult myopathic case reported.

Our cases highlight the potential for late malignant transformation and support the need for rigorous long-term hepatic monitoring in all patients with DGUOK variants, regardless of their initial clinical presentation. These non-invasive measures may be crucial for detecting early oncogenic transformation and therefore improving patient outcomes through earlier intervention.

MITOCHONDRIAL DISORDERS

Abstract P045 - Cod. 143386

DEFINING OBJECTIVE AND PERSONALIZED MOTOR OUTCOMES IN PEDIATRIC MITOCHONDRIAL DISORDERS THROUGH WEARABLE SENSOR TECHNOLOGY

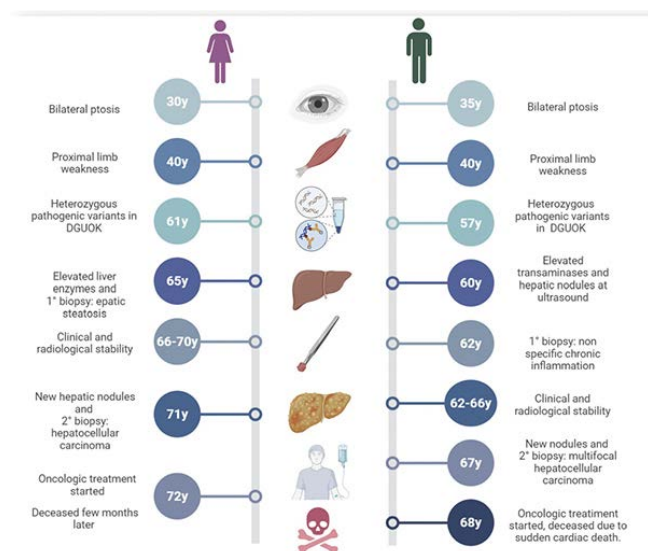
Pettenuzzo I.^{*1}, Moriani M.¹, Di Matteo K.¹, Lenzi A.¹, Sperandio F.¹, Fetta A.¹, Bisi M.C.², Stagni R.², Garone C.¹

¹ Department of Medical and Surgical Sciences, Alma Mater Studiorum - University of Bologna - IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età pediatrica, Bologna, Italy, Bologna, Italy, ² Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi", University of Bologna - Interdepartmental Center for Industrial Research on Health Sciences & Technologies, University of Bologna, Bologna, Italy

Pediatric mitochondrial diseases present with marked clinical heterogeneity and progressive motor impairment, while objective and quantifiable outcome measures remain limited. To address this gap, a protocol based on wearable inertial measurement units and surface electromyography was developed in collaboration with the Department of Electrical, Electronic and Information Engineering "Guglielmo Marconi". The protocol aims to quantitatively characterize motion patterns during 20 motor tasks (e.g. normal and tandem gait, nose-to-finger test) in pediatric patients with mitochondrial disorders. Wearable sensors are easy to use, non-invasive, and feasible in pediatric neurology, allowing quantitative monitoring in both clinical and natural environments.

The protocol is designed to be integrated into routine clinical assessment and tailored to individual motor and cognitive abilities. Less cooperative patients (e.g. young age, encephalopathy), undergo free-movement recordings, while more cooperative patients are assessed using tasks derived from neurological examination and standardized scales.

To date, 19 recordings have been collected from 12 patients (age range: 5–17 years; median: 13 years). Ten patients were assessed at baseline, while 2 underwent longitudinal recordings; 3 patients performed gait tasks using walking aids. Preliminary analyses identified statistically significant alterations in spatiotemporal gait parameters,



increased gait variability, and changes in nonlinear motor control metrics compared to healthy age-matched controls.

These results support the feasibility and sensitivity of wearable-sensor-based assessments in pediatric mitochondrial disorders. Motion metrics can represent objective and responsive outcome measures for longitudinal follow-up monitoring and endpoints in future clinical trials, enabling improved detection of motor changes and evaluation of therapeutic effects in this heterogeneous population.

MITOCHONDRIAL DISORDERS

Abstract P047 - Cod. 143462

EARLY EFFECTIVENESS AND SAFETY OF OMAVELOXOLONE IN FRIEDREICH'S ATAXIA: A REAL-WORLD STUDY FROM PALERMO

Lima S.M.*, Campo S., Rini N., Quartetti U., Caltagirone M., Mancuso P., Brighina F., Di Stefano V., Labate A.

Department of Biomedicine, Neuroscience, and Advanced Diagnostic (BIND), University of Palermo, Palermo, Italy

Friedreich's ataxia (FRDA) is an inherited disease caused by frataxin deficiency, leading to suppression of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant pathway (1). This results in oxidation-related mitochondrial stress and dysfunction. Omaveloxolone, a semi-synthetic triterpenoid drug, activates the Nrf2 pathway and is the first approved treatment for FRDA investigated in the MOXle trial (2).

This study evaluated its effectiveness and safety in our patient cohort.

Twenty patients affected by FRDA were treated with omaveloxolone and followed up for 48.2 ± 8.0 weeks. The drug was safe with no significant adverse events and without discontinuations. Indeed, asymptomatic, and transient liver transaminase elevation occurred in 50% of patients. Cardiac function was stable. Clinical scales did not show any significant difference during follow-up, but a significant reduction in IL-6 was reported.

Our results confirm current literature regarding the drug's efficacy and tolerability. Further follow-up data are needed to explore long-term effectiveness and safety.

MITOCHONDRIAL DISORDERS

Abstract P049 - Cod. 143496

FROM FOCAL CERVICAL DYSTONIA TO MULTISYSTEM NEUROLOGICAL INVOLVEMENT: A CASE OF MITOCHONDRIAL DISEASE

Vittorini M.G.*¹, Sacco S.¹, Ricci S.², Tiseo C.²

¹ *Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy*, ² *Department of Neurology and Stroke Unit of Avezzano-Sulmona, ASL 1 Avezzano-Sulmona-L'Aquila, Avezzano, Italy*

We report the case of a woman diagnosed with cervical dystonia at the age of 20. She was treated with botulinum toxin and cervi-

cal laminectomy at the age of 25 with some improvements. Over the next years, recurrence of cervical dystonia associated with progressive gait ataxia, dysphagia and dysarthria caused severe disability. She came to our clinic at the age of 51, due to worsening of these symptoms. Both her father and brothers died at young age of myocardial infarction, while her son, born with Fallot's tetralogy, passed away because of post-infective ADEM. Neurological examination showed: cognitive impairment, strength deficit with ataxia and adiadochokinesia on the left side, four limbs dysmetria, dysarthria, buccofacial dyskinesias, axial and head tremor, hypoactive deep tendon reflexes. General examination revealed short stature, muscular hypotrophy-especially in the left lower limb- and multiple lipomas. To demonstrate the heterogeneity and progressive nature of mitochondrial disorders

During the hospitalization, limb myoclonus occurred, associated with paroxysmal slow-wave EEG abnormalities, leading to the diagnosis of myoclonic epilepsy and an antiseizure therapy was started. Electrophysiological studies demonstrated a sensitive axonal polyneuropathy and a myopathic pattern at lower and upper limbs, respectively. Genetic testing for spinocerebellar ataxia and chorea was negative. Muscle biopsy showed preliminary findings consistent with mitochondrial disease. Thus, both an antioxidant therapy with Q10 coenzyme and vitamin E, and a physical treatment have been initiated with limited benefits to her motor function.

This case highlights the phenotypic heterogeneity and progressive nature of mitochondrial disorders, emphasizing the importance of considering mitochondrial disease in patients with complex movement disorders and epilepsy.

MITOCHONDRIAL DISORDERS

Abstract P051 - Cod. 143094

LATE-ONSET SEVERE AXONAL POLYNEUROPATHY IN MUTO METHYLMALONIC ACIDEMIA AFTER LIVER-KIDNEY TRANSPLANTATION: A GENOTYPE-INFORMED CASE REPORT

Griffo M.*⁴, Magri F.¹, Bernardi E.¹, Furlan F.², Menni F.³, Testa S.³, Ronchi D.⁴, Piemonte F.⁵, Gagliardi D.⁶, Parisi M.⁶, Velardo D.⁶, Moliterno N.⁶, Padelli S.⁶, Corti S.P.⁴, Comi G.P.⁶

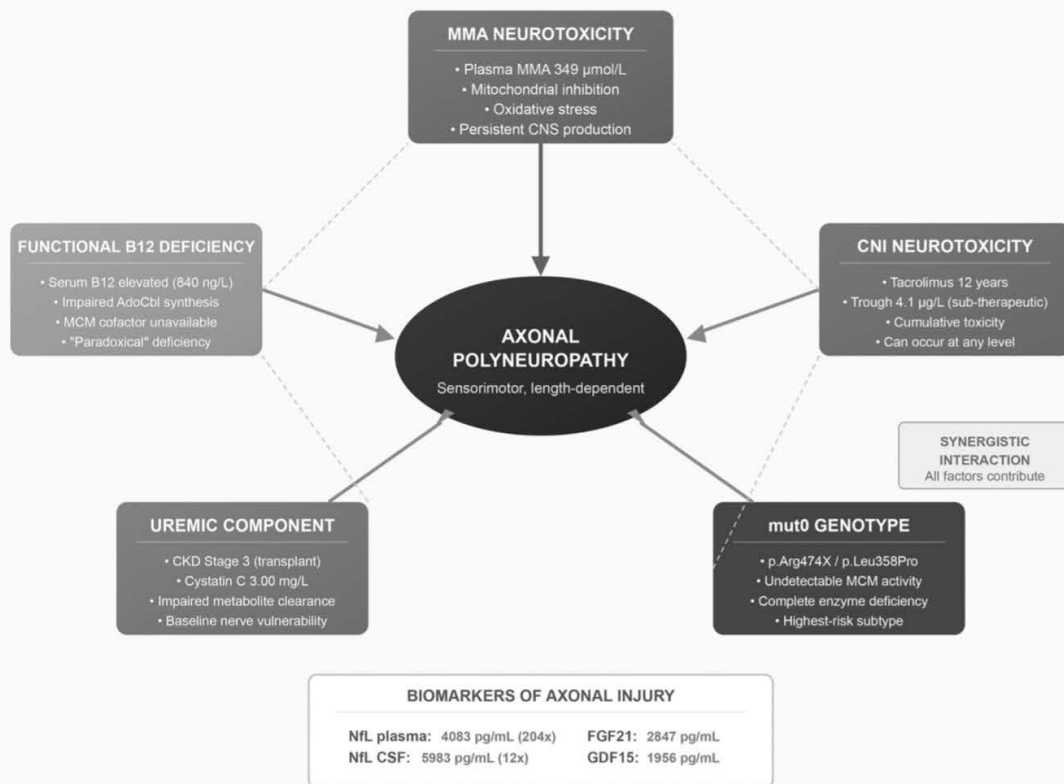
¹ *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Unità di Malattie Neuromuscolari e Rare, Milano, Italy*, ² *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Unità di Terapia Intensiva Pediatrica, Milano, Italy*, ³ *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Unità di Nefrologia Pediatrica, Milano, Italy*, ⁴ *Centro Dino Ferrari, Dipartimento di Fisiopatologia medico-chirurgica e dei trapianti, sezione di Neuroscienze, Università degli Studi di Milano*, ⁵ *IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy*, ⁶ *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Unità di Neurologia, Milano, Italy*

Liver-kidney transplantation in methylmalonic acidemia (MMA) improves metabolic control but does not eliminate neurological risk. Peripheral neuropathy is increasingly recognized in transplanted patients, yet its pathophysiology and surveillance strategies remain poorly defined.

To report a case of severe axonal sensorimotor polyneuropathy due to

Multifactorial Pathogenesis of Polyneuropathy in Post-Transplant MMA

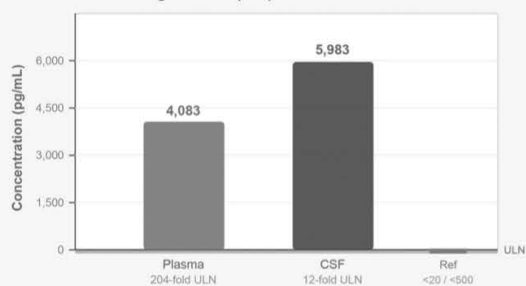
Interplay of metabolic, renal, iatrogenic, and nutritional factors in mut0 genotype



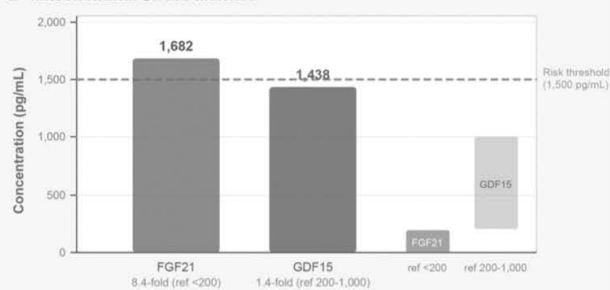
Biomarker Profile and Clinical Timeline

NfL, FGF21, and GDF15 levels at presentation with longitudinal clinical context

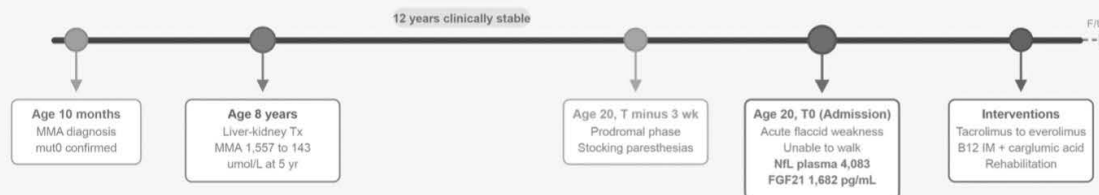
A Neurofilament Light Chain (NfL)



B Mitochondrial Stress Markers



C Clinical Timeline (relative timepoints)



■ NfL: neuroaxonal injury ■ FGF21: hepatic mitochondrial stress ■ GDF15: mitochondrial integrated stress response ■ Normal reference range

methylmalonic acidemia caused by compound heterozygous mutations of MMUT gene 12 years after liver-kidney transplantation and discuss its differential diagnosis with other metabolic and iatrogenic neuropathies.

The study revealed severe axonal sensorimotor polyneuropathy with active denervation. Cerebrospinal fluid analysis and neuroimaging investigations were found to be within normal limits. Serum biomarkers revealed striking abnormalities, with FGF21, GDF15 and NFL being highly elevated. The pathogenesis of polyneuropathy appeared multifactorial, involving factors like functional vitamin B12 deficiency, chronic kidney disease with accumulation of nephrotoxic substances, neurotoxicity of methylmalonic acid, and tacrolimus-induced neurotoxicity. Treatment consisted in immunosuppressive switch from tacrolimus to everolimus, administration of vitamin supplements, carnitine, and rehabilitation.

Severe peripheral neuropathy in MMA patients could occur even after long periods of post-transplant metabolic stability, especially in patients carrying the mut0 genotype determining complete enzyme deficiency. Electrophysiological characterization is essential for differential diagnosis. Further diagnostic investigations should not miss the metabolic, nephrotoxic, and iatrogenic factors, taking into account the potential neurotoxicity even at therapeutic blood levels. This case emphasizes the predisposition of MMA patients with MMUT deficiency to develop neurological complications, even after long periods of metabolic stability post-liver-kidney transplant, and highlights the need for genotype-based surveillance for early detection of subclinical neuropathy in these patients.

MITOCHONDRIAL DISORDERS

Abstract P053 - Cod. 143111

NATURAL HISTORY AS A ROADMAP FOR THERAPEUTIC DEVELOPMENT IN MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY

Pettenuzzo I.^{1*}, Arena I.G.², Harrison E.², Biggs H.², Van Den Ameele J.³, Garone C.¹

¹ Department of Medical and Surgical Sciences, Alma Mater Studiorum - University of Bologna; IRCCS Istituto delle Scienze Neurologiche di Bologna, U.O.C. Neuropsichiatria dell'età pediatrica, Bologna, Italy,

² Department of Clinical Neurosciences, University of Cambridge, UK, Cambridge, United Kingdom, ³ Department of Clinical Neurosciences, University of Cambridge; MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, United Kingdom

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an ultra-rare, autosomal recessive disorder caused by loss-of-function mutations in TYMP, resulting in thymidine phosphorylase deficiency, systemic accumulation of thymidine and deoxyuridine, mitochondrial DNA instability, and progressive multisystem disease. Patients typically present with gastrointestinal symptoms in early adulthood, while almost all exhibit asymptomatic leukodystrophy and myopathy. Limited natural history data from small retrospective cohorts and case reports hinders early diagnosis, prognostic stratification, and the design of clinical trials for emerging disease-modifying

therapies.

The aim of this study is to comprehensively characterize the clinical course, phenotypic variability, biomarkers, genotype-phenotype correlations, and treatment outcomes in patients with biochemically or genetically confirmed MNGIE worldwide.

We established a multicenter, international, retrospective natural history study collecting standardized, anonymized data from clinicians caring for MNGIE patients. Data include demographics, genetics, biochemical assays, longitudinal clinical features, imaging, histology, biomarkers, and therapeutic interventions (including HSCT, liver transplantation, and enzyme-based approaches). Data are captured, after de-identification, in a secure REDCap database and supplemented by data from existing international registries.

This international study seeks to include all MNGIE cases worldwide by engaging clinicians, enabling a detailed characterization of disease onset, progression, and survival; identification of predictors of disease course; and evaluation of outcomes associated with current therapeutic strategies. This coordinated international effort will define disease trajectories, highlight predictors of progression, and directly guide the timing, selection, and assessment of current and future therapies, providing essential data to optimize patient management and support outcome-driven interventional studies. For any further information, please contact us at add-tr.mitoteam@nhs.net.

MITOCHONDRIAL DISORDERS

Abstract P055 - Cod. 143397

SANDO SYNDROME IN SIBLINGS: A FAMILIAL CASE SERIES OF POLG-RELATED DISORDER

Petrosino A.^{1*}, Pauro A.¹, Sogus E.¹, Capece G.¹, Fornasier T.¹, Marcon M.², Deluca C.³, Bello L.¹, Pegoraro E.¹, Minicuci G.M.⁴

¹ Department of Neurosciences, University of Padova, Padova, Italy, ² Neurology, 'Cazzavillan' Hospital, Arzignano, Vicenza, Italy, ³ Neurology, 'San Bortolo' Hospital, Vicenza, Italy, ⁴ Clinica Neurologica, Padova University Hospital, Padova, Italy

POLG encodes the mitochondrial DNA polymerase and mutations in POLG represent the most common cause of inherited mitochondrial disorders and can lead to early-onset mtDNA depletion or later-onset phenotypes due to mtDNA deletions. Clinical presentations are highly heterogeneous and include the ataxia-neuropathy spectrum (ANS), encompassing sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia, collectively known as SANDO.

We report three siblings diagnosed with SANDO.

The first patient developed symptoms at age 40, with progressive ataxia, ptosis, and ophthalmoparesis, followed by dysphagia and dysarthria. Muscle biopsy revealed mitochondrial abnormalities, and electromyography showed severe sensory axonal neuropathy. Genetic testing identified compound heterozygous POLG mutations (c.1399G > A and c.2243G > C), confirming SANDO. Over time, the patient developed frequent falls, epileptic seizures, and progressive cognitive impairment, and died at age 60 from complications related to prolonged immobility. The second patient, a 41-year-old woman with psychiatric symptoms treated with valproate, was evaluated for a 10-year history of progressive ataxia. Brain MRI showed bilat-

eral bulbar hyperintensities. Electromyography demonstrated severe sensory axonal neuropathy. Following her brother's diagnosis, genetic testing confirmed the same POLG mutations, and valproate was discontinued. Her neurological condition progressively worsened, leading to bedridden status. The third patient, a 56-year-old man, presented with imbalance and dysarthria. Neurological examination showed mild ataxia and ophthalmoparesis. Genetic testing confirmed the same compound heterozygous POLG mutations. This family illustrates the phenotypic variability of autosomal recessive POLG-related SANDO, with differing clinical severity. Genetic testing of the parents was unavailable, preventing determination of whether the mutations were in cis or in trans.

THURSDAY, MAY 14TH, 2026

POSTER SESSION

Spinal Muscular Atrophy and other neuromuscular disorders | odd numbers

15:00-16:30

Chairs: Letizia Manneschi, Elisabetta Sette

ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Abstract P001 - Cod. 143217

HARMONIZATION OF MULTI-STACK MUSCLE MRI FOR RADIOMIC ANALYSIS

Amore D.¹, Tran H.E.², Boccia E.², Bono F.², Sampiero M.², Santini F.³, Diaz--Manera J.⁴, Verdu--Diaz J.⁴, Boldrini L.², Monforte M.^{*1}
¹ UOC di Neurologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Roma, Italy, ² Radiomics GStEP Core Research Facility, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Roma, Italy, ³ Basel Muscle MRI, Department of Biomedical Engineering, University of Basel, Basel, Switzerland, Basel, Swaziland, ⁴ John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom, Newcastle upon Tyne, United Kingdom

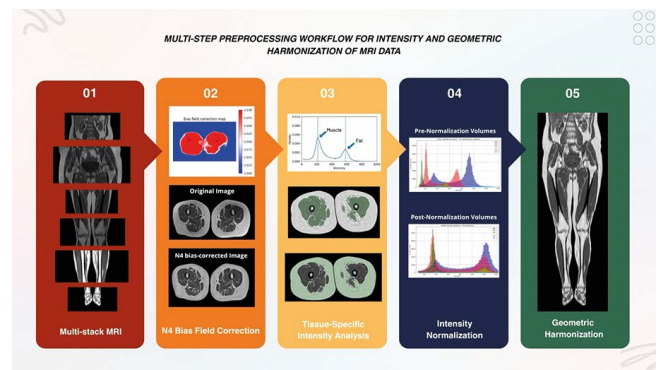
Muscle MRI datasets acquired using multi-stack protocols and different MRI scanners are frequently affected by intensity inhomogeneities, inter-scan signal variability, and spatial misalignment, limiting direct comparison across acquisitions.

Within the Telethon–UILDM funded DEAL-FSHD project (GUP 24001), this work aims to develop a standardized muscle MRI preprocessing pipeline to enable robust radiomic analyses and predictive modeling of disease progression. Specifically, we present a semi-automated pipeline designed to normalize signal intensity and correct geometric inconsistencies in heterogeneous muscle MRI data. Each MRI stack is processed using a Python-based pipeline. Processing includes N4 bias field correction, extraction of the anatomical region of interest, and tissue-specific intensity analysis to discriminate muscle and fat

components. Intensity normalization is performed through expert-guided selection of tissue-specific percentiles, which are linearly mapped to predefined pseudo-T1 reference values, ensuring reproducible signal harmonization across heterogeneous acquisitions. Spatial inconsistencies are addressed by affine-based realignment, slice reordering according to real-world Z-coordinates, and in-plane resampling when required.

The processing pipeline for each DICOM volume requires a mean of 41 s per stack (± 13.9 s), showing moderate variability across the analyzed volumes. Normalization effectiveness was confirmed by a strong reduction in inter-stack coefficient of variation of tissue intensity peaks.

We developed a fast and robust pre-processing pipeline able to generate a single, geometrically coherent 3D volume as output, immediately suitable for the segmentation process and radiomic analysis.



ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING

Abstract P003 - Cod. 143019

THE COMPASS-NMD NEUROMUSCULAR GENOME ATLAS: A NEW AI-BASED PLATFORM FOR ADVANCED DEEP PHENOTYPING AND STRATIFICATION IN HEREDITARY NEUROMUSCULAR DISORDERS

Nuredini A.^{*1}, Corrias R.², Mendelsohn D.³, Pini S.¹, Garzo Manzanares A.⁶, Scipioni M.P.², Obach M.⁶, Laporte J.⁹, Savarese M.⁷, Diaz Manera J.⁸, Straub V.⁸, Polanska J.⁵, Santorelli F.M.⁴, Schoser B.³, Tupler R.¹

¹ Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Modena, Italy, ² Fincons Group, Lugano, Switzerland, ³ Friedrich-Baur-Institut, Department of Neurology, Ludwig Maximilian University (LMU), Munich, Germany, ⁴ Molecular Medicine for Neurodegenerative and Neuromuscular Diseases Unit, IRCCS Fondazione Stella Maris, Pisa, Italy, ⁵ Department of Data Science and Engineering, Silesian University of Technology, Gliwice, Poland, ⁶ Tecnalia Research and Innovation, San Sebastian, Spain, ⁷ Folkhälsan Research Center, Helsinki, Finland, ⁸ John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle Hospitals NHS Foundation Trust, Newcastle University, Newcastle Upon Tyne, United Kingdom, ⁹ Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC), Université de Strasbourg, Illkirch, France

Hereditary neuromuscular disorders (HNMDs) are characterized by

marked clinical and molecular heterogeneity, which limits accurate diagnosis, prognosis, and patient stratification for clinical trials. Addressing these challenges requires large-scale, harmonized, and interoperable integration of multimodal clinical and molecular data across centers and countries.

The CoMPaSS-NMD Neuromuscular Genome Atlas (NMDGA) aims at establishing a federated, GDPR-compliant infrastructure to integrate multimodal data and enable ontology-driven and AI-ready patient stratification. The Atlas integrates collected clinical, genetic, histopathological, and MRI data from 500 undiagnosed patients and deploys AI-based analytical tools that were developed and trained using large retrospective cohorts.

The NMDGA collects deep phenotypic, genetic, histopathological, and MRI data from 500 newly recruited myopathic patients without a definitive diagnosis. The platform adopts a metadata-driven architecture that allows secure data discovery without centralizing sensitive raw data. Clinical phenotypes collected through a structured electronic case report form (> 200 parameters) were systematically mapped to the Human Phenotype Ontology (HPO), resulting in the integration of 203 HPO terms and the proposal of eight novel neuromuscular-specific terms. This semantic layer enables hierarchical phenotype navigation, ontology-aware filtering, and cross-domain queries combining phenotypic, genetic, imaging, and histopathological features.

The CoMPaSS-NMD Atlas provides a shared, web-accessible resource for multimodal neuromuscular data, integrating harmonized phenotypes with computational analysis and visualization tools. The NMDGA deep phenotyping enables precise cohort definition, improved genotype-phenotype correlation, and robust patient stratification, supporting translational research and future clinical trials in neuromuscular diseases.

OTHERS

Abstract P161 - Cod. 143206

A NEW MATHEMATICAL MODEL REVEALS NON-RANDOM RELATIVE SYNONYMOUS CODON USAGE VALUES IN A COHORT OF SYNONYMOUS VARIANTS IN NEUROMUSCULAR AND CARDIAC GENES

Mietto M.*², Tonelli L.², Sanchini M.², Blazej P.¹, Ferlini A.²

¹ Department of Bioinformatics and Genomics, Faculty of Biotechnology, University of Wrocław, Wrocław, Poland, ² Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Synonymous variants can affect RNA structure and stability, splicing, miRNA binding, translational speed, and co-translational protein folding. However, their functional significance remains elusive, and they are often classified as variants of uncertain significance or likely benign, limiting comprehensive genome interpretation.

We reanalysed 283 Next Generation Sequencing datasets from large cardiac and neuromuscular panels, and we focused on synonymous changes occurring in 51 genes, standing alone without any other known class IV or V variants.

We applied a Codon Block Recoding (CBR) model, which classifies

codons into six frequency-based groups, ranging from very frequent to very rare, according to relative synonymous codon usage (RSCU). This approach aims to address the functional meaning of synonymous changes. Synonymous changes were scored by calculating the distance between codon classes before and after the nucleotide change.

A total of 72 and 118 synonymous variants were identified in 19 myogenic and 32 cardiogenic genes, respectively. Variants with a class distance ≥ 3 were prioritized, resulting in 14 myogenic and 21 cardiogenic synonymous changes. Surprisingly, 26 of these variants involved changes from "fastest/frequent" to "slowest/rare" codons (Codon Adaptation Index-CAI negative), while 9 involved changes from "slowest/rare" to "fastest/frequent" codons (CAI positive).

By applying the CBR model, we highlighted a few synonymous changes varying their RSCU values by changing from frequent to rare codons and vice versa. These unexpected results may suggest a potential impact on translational efficiency. Functional studies to assess the pathogenicity scores of these synonymous changes are ongoing.

OTHERS

Abstract P163 - Cod. 142905

ACUTE UNILATERAL HYPOGLOSSAL NERVE PALSY SECONDARY TO HYPOGLOSSAL CANAL SCHWANNOMA: A CASE REPORT

Terenghi F.*¹, Politi L.S.², Gallo C.¹, Nobile--Orazio E.³

¹ Neuromuscular and Neuroimmunology Unit, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089 Rozzano – Milan, Italy., Rozzano-Milan, Italy, ² Department of Neuroradiology, IRCCS Humanitas Research Hospital, Via Manzoni 56, 20089 Rozzano-Milan, Italy, Rozzano-Milan, Italy, ³ Department of Medical Biotechnology and Translational Medicine, Milan University, Milan, Italy., Rozzano-Milan, Italy

Isolated hypoglossal nerve palsy generally presents dysphagia, dysarthria, and tongue wasting. The common etiologies are tumor, trauma, vascular lesions, infections, demyelinating disorders, and idiopathic.

-

A 82 year old woman presented to ER reporting the acute onset of speech and tongue movements difficulties with right temporal-parietal headache. Neurological examination showed dysarthria and mild hyposthenia of the tongue right side. Brain CT and CT angiography were normal. Brain MRI scan revealed a non-specific 5 mm fluid layer along the contours of the right petrous bone extending into the right hypoglossal. CMAP of the right hypoglossal nerve was not evoked and the needle examination no showed denervation. The transcranial evoked potentials showed no alterations in amplitude and latency, repetitive stimulation was negative. A diagnosis of idiopathic hypoglossal mononeuropathy was hypothesised. At the one-month check-up, the patient reported disappeared the headache but that she had greater difficulty moving her tongue and speaking. At the three-month check-up the examination revealed a rightward deviation of the protruding tongue with marked hypotrophy. The brain MRI scan at 6 months showed the presence of a small formation along the nerve tract in the hypoglossal canal, suggestive of a schwannoma.

The patient was started on gamma knife treatment.

The onset of compressive paralysis usually follows a progressive course. In our case, the acute onset led us to hypothesise idiopathic paralysis, but the subsequent worsening, particularly of the atrophy, prompted us to investigate further, leading to the discovery of a small schwannoma inside the hypoglossal canal.

OTHERS

Abstract P165 - Cod. 143400

ADPRS AND STRESS-TRIGGERED NEURODEGENERATION: THREE NOVEL VARIANTS

Comisi F.F.*², Travaglini L.¹, Catteruccia M.², Tosi M.², De Luca G.², Mizzoni I.², Fanfoni C.³, Staccioli S.³, D'Amico A.², Diodato D.²
¹ Laboratory of Medical Genetics, Translational Cytogenomics Research Unit, Bambino Gesù Children Hospital IRCCS, Roma, Italy, ² Muscular and Neurodegenerative Diseases, Bambino Gesù Children Hospital IRCCS, Roma, Italy, ³ Unit of Neurorehabilitation, Bambino Gesù Children's Hospital, IRCCS, Roma, Italy

Biallelic variants in ADPRS cause a rare disorder characterized by stress-induced childhood-onset neurodegeneration with variable ataxia and seizures (CONDSIAS). ADPRS encodes an ADP-ribosylhydrolase, which removes the post-translational addition of poly-ADP riboses from proteins in the cellular stress response pathway. Since its first description in 2018, genotype-phenotype correlations remain incompletely defined.

We describe two unrelated children with progressive neurodegeneration and stress-associated deteriorations. Whole-exome sequencing (WES) was performed, and variants were classified according to ACMG criteria. A structured PubMed search identified 59 patients reported to date.

Case 1: A male child presented in infancy with developmental delay, febrile seizures, and recurrent paroxysmal neck dystonia. At 2 years, an infection-triggered crisis was followed by rapid loss of ambulation and progression to respiratory failure requiring tracheostomy and long-term invasive ventilation. Brain MRI showed bilateral posterior putaminal involvement with an extensive spinal cord signal abnormality. NCS revealed severe axonal sensorimotor polyneuropathy. WES identified compound heterozygous ADPRS missense variants c.74G > T (p.Gly25Val) and c.827C > T (p.Ser276Leu), both likely pathogenic. Case 2: A female child developed early gait instability and strabismus, followed by severe stress-associated cardiorespiratory collapse with prolonged ventilator dependence, evolving to spastic-dystonic tetraparesis, gastrostomy feeding, recurrent respiratory exacerbations, and death at 10 years. WES identified compound heterozygous truncating ADPRS variants c.316C > T (p.Gln106Ter; pathogenic) and c.827dup (p.Val277GlyfsTer17).

These cases expand the molecular landscape of CONDSIAS, with three novel variants. Phenotype in our patients is concordant with literature description. Nevertheless, a prompt diagnosis could be tricky since the presence of stress-induced deterioration can mimic mitochondrial disorders

OTHERS

Abstract P167 - Cod. 143074

BEYOND THE DIAGNOSIS: AFFECTIVITY AND SEXUALITY IN NEUROMUSCULAR DISORDERS. RESULTS FROM THE EROS-NMD QUESTIONNAIRE

Sardi A.¹, Gizzi G.*¹, Biolcati Rinaldi A.², Pugliese M.³, Brolatti N.⁴, Panicucci C.⁴, Pedemonte M.¹, Striano P.⁵, Venturino C.², Bruno C.⁶, Trucco F.⁵

¹ Pediatric Neurology and Muscular Diseases Department, IRCCS Giannina Gaslini Institute, Genoa, Italy, ² Psychology Unit (UOSD), IRCCS Giannina Gaslini Institute, Genova, Italy, ³ Parent Project APS, Rome, Italy, ⁴ Translational and Experimental Myology Center, IRCCS Giannina Gaslini Institute, Genoa, Italy, ⁵ Pediatric Neurology and Muscular Diseases Department - Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DiNOGMI), Genoa, Italy, ⁶ Translational and Experimental Myology Center, IRCCS Gaslini Institute - Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Health (DiNOGMI), Genoa, Italy

Affectivity and sexuality are key components of psychosocial development and quality of life. In neuromuscular diseases, these dimensions remain underexplored in clinical practice.

To develop a questionnaire to explore affective, relational and sexual experiences and to identify the associated needs in adolescents and young adults with neuromuscular disorders.

Twenty-six participants (mean age 23±4.9 years; 21 males) were included; 18 had either Duchenne (n = 16) or Becker (n = 2) muscular dystrophy, 8 had other muscular diseases, including spinal muscular atrophy (SMA, n = 6). Total median score was 16.8±6.1 out of 29, suggesting moderate affective-relational needs. No differences emerged across neuromuscular diagnoses, while a higher vulnerability was observed in patients at more advanced disease stages. Body experience and intimacy (score 4.9±2.4 out of 9) and support need (score 4.7±2.8 out of 10) represented the weakest domains. See Figure 1.

This exploratory study highlights both affective-relational vulnerability and personal resources in young people with neuromuscular diseases. EROS-NMD may support the identification of psychosocial needs; ongoing work is aimed to refine and standardize this tool.

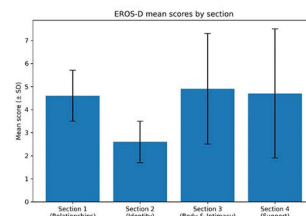


Figure 1. Mean (± SD) EROS-NMD sub-scores across the sample (N = 26), showing affective relationships and sexual identity show relatively better integration, whereas body experience and intimacy and access to information and support mainly fall within the partial adaptation/support range

OTHERS

Abstract P169 - Cod. 143423**BIALLELIC LOSS-OF-FUNCTION VARIANTS IN MYLK3 AS A CAUSE OF EARLY-ONSET RECESSIVE DILATED CARDIOMYOPATHY**

Onore M.E.*¹, Di Letto P.¹, Borrelli R.N.¹, Del Vecchio Blanco F.², Vicidomini G.¹, Palmieri F.P.¹, Spanpanato C.², Giacobbe C.², Torella A.¹, Nigro V.¹, Piluso G.¹

¹ Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Napoli, Italy, ² U.O.S.D. Genetica Medica e Cardiologia, A.O.U. Luigi Vanvitelli, Napoli, Italy

Dilated cardiomyopathy (DCM) is a condition with a broad genetic basis, involving genes that are essential for sarcomere mechanics, RNA processing, and cytoskeletal organization. MYLK3, which encodes a kinase that phosphorylates cardiac myosin heavy and light chains, may play a crucial role in cardiac function. It is highly expressed in the ventricle and promotes sarcomere organization and enhances cardiomyocyte contractility in mouse models. While MYLK3 has not yet been associated with any disease, the loss of this kinase in both mice and zebrafish induces cardiac dysfunction and heart failure. This evidence suggests that MYLK3 is essential for maintaining cardiac homeostasis.

We investigated the molecular basis of early-onset DCM in a seven-month-old infant born to healthy, unrelated parents using a Next Generation Sequencing approach.

Exome sequencing identified two loss-of-function (LoF) compound heterozygous variants in MYLK3 [NM_182493.3:c.618dup; p. (Ile207Hisfs*9) and c.1784del; p. (Gly595Valfs*14)], both of which were classified as VUS according to the ACMG criteria. LoF variants in MYLK3 have been reported in autosomal dominant familial DCM. Recently, an autosomal recessive inheritance pattern for MYLK3 was reported in three DCM patients born to consanguineous parents. Biallelic variants in MYLK3 appear to be associated with an earlier-onset and more severe phenotype than monoallelic forms.

Our results consolidate the involvement of MYLK3 in cardiomyopathies and expand its mutational spectrum. These findings provide evidence for an emerging recessive model of inheritance in pediatric DCM and highlight the clinical necessity of comprehensive genetic screening in early-onset cases.

OTHERS

Abstract P171 - Cod. 143332**BIOCHEMICAL AND IMMUNOLOGICAL MARKERS ASSOCIATED WITH THE CLINICAL RESPONSE IN ANTI-HMGCR IMMUNE-MEDIATED NECROTIZING MYOPATHY**

Barone C.*¹, Faedo E.¹, Bavestrello G.¹, Vollaro A.F.M.¹, Pesce G.², Schenone A.³, Grandis M.³

¹ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), University of Genoa., Genoa, Italy, ² Autoimmunity Laboratory, IRCCS AOM Ospedale Policlinico San

Martino, Genova, Italy, ³ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), University of Genoa - IRCCS AOM Ospedale Policlinico San Martino, Genova, Italy

Immune-mediated necrotizing myopathy (IMNM) is a severe inflammatory myopathy characterized by proximal muscle weakness, markedly elevated serum creatine kinase (CK) levels, and the presence of anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) autoantibodies. We retrospectively evaluated our patient cohort to correlate CK value and antibody titers with one-year of clinical response.

We performed a retrospective descriptive analysis of 16 patients with anti-HMGCR-positive IMNM. Collected data included demographics, statin exposure, clinical phenotype (MRC scale), and therapeutic strategies. Treatment efficacy was assessed through longitudinal evaluation of muscle strength, CK levels, and antibody titers comparing baseline with 12-month follow-up.

The cohort showed a mean age at onset of 58.5 ± 15.6 years. Statin-unexposed patients represented 37.5% of the cohort and were exclusively female ($p = 0.011$), with a trend toward younger age at onset (48.0 vs. 63.5 years). Clinical presentation at baseline was homogeneous, characterized by proximal weakness. At diagnosis, mean CK levels were elevated ($8,019 \pm 7,826$). At onset, 81.3% received combined therapy including corticosteroids (87.5%), IVIg (81.3%) and immunosuppressants (37.5%). At the follow-up, a reduction in mean CK levels was observed ($662 \pm 1,181$ U/L; $p < 0.001$). This improvement was paralleled by a significant decrease in anti-HMGCR antibody titers ($p = 0.031$). Clinically, 50% of patients achieved full strength recovery.

Our findings suggest that anti-HMGCR IMNM presents with an aggressive biochemical profile and may occur independently of statin exposure. Longitudinal monitoring of CK levels and anti-HMGCR titers appears to be a sensitive approach for assessing therapeutic response.

OTHERS

Abstract P173 - Cod. 143266**CHEMOTHERAPY INDUCED PERIPHERAL NEUROTOXICITY: PATIENT AND PHYSICIAN-REPORTED OUTCOME MISMATCH**

Alberti P.*¹, Argyriou A.², Cavaletti G.¹, Goldstein D.³, Li T.⁴, Park S.⁴, Velasco R.⁵, Bruna J.⁵, Ci--Perinnoms And Icavs Investigators W.⁶

¹ University of Milano-Bicocca, Monza, Italy, ² General Hospital of Kos Island, Dept of Internal Medicine, Kos, Greece, ³ Prince of Wales Hospital and University of New South Wales, Sydney, Australia, ⁴ Faculty of Medicine and Health, School of Medical Sciences, University of Sydney, Sydney, Australia, ⁵ Neuro-Oncology Unit, Bellvitge University Hospital - Catalan Institute of Oncology (ICO), Bellvitge Biomedical Research Institute (IDIBELL); L'Hospitalet, Barcelona, Spain, ⁶ Study Group, Milan, Italy

Chemotherapy induced peripheral neurotoxicity (CIPN) is a frequent complication of anticancer therapy and significantly affects patients' quality of life (QOL). Although QOL generally worsens with greater neuropathy severity, individuals placed in the same clinical grade of

ten show notable differences in their symptom reports. This study examined how patient reported outcome (PRO) scores vary within each neuropathy grade and evaluated whether age, sex, or chemotherapy type contribute to this variability.

Data were obtained from several prospective cohorts, including ICAVS, In Focus Australia, and CI PeriNomS II. PROs were assessed using the EORTC QLQ CIPN20 in the primary sample ($n = 413$) and the FACT/GOG NTX in a secondary sample ($n = 471$). CIPN severity was graded with NCI CTCAE and TNSc criteria. Within grade analyses used a location scale modelling framework combining ordinary least squares for mean scores with log variance models to characterize dispersion, supported by Brown–Forsythe tests.

In the EORTC QLQ CIPN20 cohort, dispersion increased steadily across NCI grades. Mean PRO scores were not associated with demographic or treatment factors, while chemotherapy type contributed to variability in grades 0–2 and sex in grade 0. In the FACT/GOG NTX cohort, chemotherapy influenced both mean scores and variability in selected grades, though overall explained variance remained low. These findings show that PRO scores vary widely even within the same clinical grade, including grade 0, suggesting that grading systems may underestimate patient burden. Chemotherapy emerged as the most consistent, albeit modest, factor contributing to within grade heterogeneity.

OTHERS

Abstract P175 - Cod. 143414

CHIKUNGUNYA-RELATED SENSORY NEUROPATHY: A CASE REPORT

Trovarelli G.*, Furia A., Liguori R., Donadio V.

Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy

Chikungunya virus infection is typically associated to painful symptomatology due to polyarthralgia and inflammatory arthritis. While rare, neurological involvement in chikungunya is possible: peripheral involvement has been mostly associated to acute pictures such as Guillain-Barré syndrome. We present a case of a patient developing large-fiber sensory polyneuropathy after chikungunya infection, as well as pain with neuropathic features that can be attributed to small fiber involvement.

Patient is a 55-year-old female who developed persistent diffuse polyarthralgia-like pain, for which she sought medical attention one month after symptom development. Due to seasonal and regional features consistent with arboviral infection, a full panel disclosed chikungunya infection. Upon further investigation, pain was found to also have burning characteristics at lower limbs, associated to tingle-like paresthesia.

Nerve conduction studies with near-nerve technique disclosed bilaterally reduced amplitudes of sural nerve responses consistent with sensory axonal polyneuropathy. Blood screening revealed no other suggestive cause of such neuropathy. Skin biopsy was also at leg and thigh performed and demonstrated reduced intraepidermal nerve fiber density consistent with small nerve fiber involvement.

Chikungunya virus infection can be associated to both large and

small nerve fiber involvement, causing sensory symptomatology that could be missed due to the more known painful picture associated to joint involvement. Thus, pain should be always be well-characterized to exclude neuropathic features.

OTHERS

Abstract P177 - Cod. 143516

CHRONIC S1 RADICULOPATHY ASSOCIATED WITH UNILATERAL CALF HYPERTROPHY AND PERSISTENT HYPERCKEMIA: A CASE REPORT

Liberatoscioli E.*, Di Muzio A.

Department of Neurology, "SS Annunziata" Hospital. Center for Neuromuscular Disease, Chieti, Italy

Persistent hyperCKemia is a frequent finding in neurological practice and may reflect either primary muscle disorders or neurogenic conditions, including peripheral neuropathies and chronic radiculopathies. Although lumbosacral radiculopathies are typically associated with muscle atrophy, focal muscle hypertrophy is rare.

The association of chronic radiculopathy, unilateral calf hypertrophy, and hyperCKemia is poorly represented in the literature and may mimic a primary myopathy.

A 37-year-old man was referred for neurological evaluation because of incidental hyperCKemia (up to 800 U/L), confirmed on repeat testing at rest. Previous creatine kinase levels had been normal. His history included right L5–S1 radiculopathy treated surgically in 2021. Postoperatively, he developed progressive enlargement of the right calf, frequent nocturnal cramps, and hypoesthesia in the S1 dermatome. Electromyography showed chronic neurogenic changes consistent with right S1 radiculopathy, and muscle MRI revealed selective hypertrophy of the right calf muscles without evidence of myopathy. Neurological examination demonstrated calf hypertrophy, S1 sensory deficit, and absence of the ipsilateral Achilles tendon reflex, with preserved strength.

Chronic S1 radiculopathy may present with focal muscle hypertrophy and persistent hyperCKemia in the absence of a primary myopathy. Neurogenic hypertrophy may result from compensatory motor unit hyperactivity, aberrant fiber overstimulation, neurogenic remodeling, and focal myositis secondary to chronic denervation. The inflammatory component, documented histologically in similar cases, may respond to corticosteroid therapy. In patients with unilateral calf asymmetry and hyperCKemia, a structured diagnostic approach integrating neurological examination, EMG and targeted imaging is essential to recognize neurogenic hypertrophy.

OTHERS

Abstract P179 - Cod. 142856

CLINICAL EVALUATION OF MUSCLE IMPAIRMENT USING ULTRASOUND RADIOMICS TECHNIQUES AND FUNCTIONAL TESTS IN INCLUSION BODY MYOSITIS

Monte A.*, Bizet B., Paola T., Borin G., Cheli M., Zamparo P., Vattermi G.

Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona., verona, Italy

Sporadic Inclusion Body Myositis (sIBM) is a progressive acquired myopathy that typically affects adults over 50. The diagnosis is challenging because the current clinical and morphologic criteria are specific but not highly sensitive. Quantitative Ultrasound Radiomics (QUR) enables objective characterisation of muscle tissue by analysing ultrasound wave propagation in biological tissues and, when combined with functional assessments, may improve sIBM diagnosis and monitoring.

This study aimed to investigate the utility of QUR techniques together with a functional evaluation in sIBM.

Nineteen sIBM patients and seventeen control subjects participated in a single experimental session. Upper and lower limb functional capacity was assessed using an isometric chair, along with ultrasound evaluation of the biceps brachii, triceps brachii, vastus lateralis, tibialis anterior, and medial gastrocnemius muscles. Disease severity was assessed using the IBM-FRS. Hamstring-to-quadriceps (H:Q) and elbow extension-to-flexion (E:F) strength ratios were calculated from maximal isometric forces. From ultrasound images, 257 radiofrequency-based radiomics features were extracted, and feature selection was performed using a LASSO machine-learning approach. H:Q was significantly higher in sIBM patients than in controls and was positively correlated with IBM-FRS, whereas no association was observed for the E:F ratio. The final QUR model demonstrated high diagnostic performance (AUROC > 0.78) and strong association with disease severity ($R^2 = 0.89$). When combined, the H:Q ratio and QUR achieved excellent diagnostic accuracy (AUROC > 0.89), with high specificity (> 92%) and no false positives.

QUR, particularly when combined with a simple functional assessment, is a promising tool for diagnosing and monitoring sIBM.

OTHERS

Abstract P181 - Cod. 143349

DIAGNOSTIC CHALLENGES OF SEVERE RHABDOMYOLYSIS IN THE BURN ICU: INSIGHTS FROM A PEDIATRIC CASE

Lombardi M.*¹, Velardo D.², Moggio M.², Moliterno N.³, Alberti C.⁴, Comi G.P.⁴, Corti S.P.⁴

¹Neurology Unit, AOU Maggiore della Carità, Department of Translational Medicine, University of Eastern Piedmont, Novara, Italy, ²IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular and Rare Disease Unit, Milan, Italy, ³IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy, ⁴Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Rhabdomyolysis is a potentially life-threatening condition with a broad etiological spectrum. In critically ill burn patients, common triggers are often identifiable; however, less frequent causes may be overlooked, particularly in complex intensive care settings.

To report an unusual case of severe rhabdomyolysis in a critically

ill pediatric burn patient with atypical neurophysiological and histopathological findings, and to frame it within less common etiologies of rhabdomyolysis in the intensive care setting.

A 16-year-old male with extensive flame burns involving 45% total body surface area was admitted to the ICU and required deep sedation and invasive support. Early serum creatine phosphokinase (CPK) levels were within the normal range. The clinical course was complicated by Haemophilus influenzae pneumonia with acute hypoxemic respiratory failure and by Propofol Infusion Syndrome, associated with cardiac biomarker elevation and ventricular tachycardia, in the absence CPK increase. On day 14 of ICU stay, a sudden onset of severe rhabdomyolysis occurred, with CPK levels exceeding 50,000 U/L; medical and family history were unremarkable.

Neurophysiological assessment, limited by critical illness, showed diffuse denervation activity with near-complete absence of voluntary motor unit recruitment and a proximodistal gradient with relative distal sparing, suggesting a primary myopathic process. Myositis-related autoantibodies were negative, and muscle biopsy revealed isolated necrotic fibers without significant inflammatory infiltrates and preserved muscle architecture.

Rhabdomyolysis in critically ill burn patients may arise from uncommon and multifactorial mechanisms, underscoring the diagnostic complexity of ICU-associated myopathic processes and the need for a systematic, integrated clinical, neurophysiological, and pathological approach.

OTHERS

Abstract P183 - Cod. 143082

EVIDENCE FROM LITERATURE AND REAL-WORLD DATA: A GENDER MEDICINE PERSPECTIVE ON PERIPHERAL NERVE DISORDERS

Daddoveri F.*, Schirizzi E., Montano V., Bravi C., Viola D.V., Ricci G., Mancuso M., Siciliano G.

Neurological Clinic, Department of Clinical and Experimental Medicine, University of Pisa, Italy, Pisa, Italy

Gender differences shape the epidemiology, clinical presentation and treatment response of peripheral neuropathies, yet these aspects remain underexplored in real-world cohorts and clinical guidelines. Understanding such differences is essential to develop precision medicine and equitable care provision.

To synthesize current evidence on gender-related patterns in neuropathies and to validate these findings in a large tertiary-center cohort, highlighting implications for clinical practice.

A PRISMA-guided literature search across PubMed, Embase, Web of Science, and Cochrane identified 405 records; after duplicate removal, 283 full-text articles were screened. Forty-seven high-quality publications met inclusion criteria, informing a structured review of peripheral neuropathies' mechanistic and therapeutic insights. We then analyzed 435 patients from our center, stratified by gender, neuropathy subtype, etiology, and pain characteristics. Our cohort (210 women, 225 men) showed distinct subtypes distribution. Genetic neuropathies predominated in women (91 vs 64) whereas immune-

mediated forms prevailed among males (CIDP: 41 vs 36; GBS: 30 vs 16). Small fiber neuropathy was markedly more common in women (20 vs 4), as well as chemotherapy-induced neuropathy (11 vs 5), while diabetic neuropathy was higher in men (14 vs 3). Pain assessment using validated scales revealed that women reported greater symptom burden and poorer quality of life.

This study, mirroring published data, bridges a gap between literature and real-world evidence, confirming that gender is a key determinant in neuropathies' incidence, phenotype, and pain perception. Our results support for gender-stratified diagnostic pathways and tailored therapeutic strategies, addressing a critical gap in current guidelines and clinical trials, which rarely incorporate gender-specific analyses.

OTHERS

Abstract P185 - Cod. 143105

FREQUENCY AND CLINICAL FEATURES OF ANTIBODIES AGAINST THE NOVEL TARGETS MX1 AND DBNL IN SMALL FIBER NEUROPATHY

Morelli L.^{*1}, Ricciardiello F.¹, Furia A.², Incensi A.¹, Vozzi S.², Serra L.¹, Gligora I.², Vacchiano V.³, Rizzo G.³, Donadio V.¹, Liguori R.³, Giannoccaro M.P.¹

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Patologia Neuromuscolare e Neuroimmunologia, Bologna, Italy, ² Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ³ IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy

Small fiber neuropathy (SFN) is a peripheral neuropathy characterized by pain and autonomic symptoms. Although several causes are known, evidence suggests an autoimmune etiology, with few identified autoantibody targets. Antibodies against MX1, DBNL, and KRT8 have recently been proposed as potential biomarkers, but further validation is required.

This prospective observational study evaluated the frequency of MX1, DBNL, and KRT8 autoantibodies in suspected SFN patients using newly established in-house cell-based assays (CBAs).

A primary cohort of 258 consecutive suspected SFN patients was recruited and underwent blood sampling and skin biopsy. Sera were screened for MX1, DBNL, and KRT8 antibodies by fixed in-house CBAs. A confirmatory cohort of 31 idiopathic SFN (iSFN) was tested. Positive cases were clinically characterized, including symptom onset related to COVID-19 infection or vaccination. Positivity was confirmed by co-localization and immunoadsorption assays.

In the primary cohort, four patients (1.5%) were seropositive (2 MX1-IgG, 2 DBNL-IgG), with no KRT8-IgG detected. All seropositive patients showed reduced intraepidermal nerve fiber density (IENFD). MX1 cases exhibited somatic and autonomic iSFN; DBNL cases included both an autoimmune secondary SFN and iSFN with symptoms onset post-COVID-19 vaccination. In the confirmatory cohort, one patient (3.2%) tested positive for MX1-IgG, while none were positive for DBNL-IgG.

In conclusion, autoantibodies against MX1 and DBNL are rare in SFN, with no KRT8 reactivity detected. MX1-seropositive patients shared

clinical features including older age, diffuse burning pain, and pruritus, suggesting that MX1-IgG may define a distinct iSFN subtype. The confirmatory cohort supports the low frequency and an age-related immunological predisposition.

OTHERS

Abstract P187 - Cod. 143427

HAND-ER: A HEALTH NEEDS ASSESSMENT STUDY ON PATIENTS AFFECTED BY RARE PEDIATRIC-ONSET NEUROMUSCULAR DISORDERS IN EMILIA-ROMAGNA

Briganti E.^{*1}, Giannotta M.², Scarpini G.², Cordelli D.M.¹, Vacchiano V.³, Liguori R.³, Zenesini C.⁴, Catanese D.⁵, Baroni R.⁵, Pini A.²

¹ Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy, ² Pediatric Neuromuscular Unit, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ Centro Clinico NeMO, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ⁴ UO Epidemiologia e Statistica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ⁵ UOC Sistemi Informativi Aziendali, AUSL Bologna, Bologna, Italy

Regarding the Document for the organization of integrated care for people with Neuromuscular Disorders

(NMDs) in Emilia-Romagna (BURERT n. 225, 7 August 2023), we developed a healthcare organizational study called "HAND-ER" (Health Needs Assessment for Neuromuscular Disorders – Emilia-Romagna). It consists of a health needs assessment of patients affected by pediatric-onset NMDs to verify the effective adherence to Standards of Care (SoC).

We conducted a census of patients diagnosed with pediatric-onset NMDs who reside in Emilia-Romagna and have undergone at least one examination at our Pediatric Neuromuscular Unit. We identified 282 total patients. We then selected those with the least heterogeneous pathologies for which published SoC exist (i.e., 65 cases of Duchenne muscular dystrophy and 55 cases of spinal muscular atrophy, aged between 3 months and 45 years).

We described the normative health needs (i.e., published SoC) for these pathologies, recording the healthcare services to be provided (e.g., neurological examination, spirometry) and the timing of their provision (e.g., at least once a year).

We then performed a retrospective analysis of the services provided to the selected patients between 01/01/2014 and 30/06/2025 extracted from the regional data warehouse and compared them with the SoC by calculating deviation indices.

Our study shows greater adherence to SoC in pediatric age than in adulthood.

We emphasize the importance of the tertiary referral center in prescribing healthcare services according to SoC and the need to optimize pathways for rare pediatric-onset NMDs within the tertiary center and proximity care facilities, especially during the transition to adulthood.

OTHERS

Abstract P189 - Cod. 143376**MORE THAN A SMILE: STRUCTURED ORAL HYGIENE STRATEGIES TO IMPROVE CARE IN NEUROMUSCULAR DISEASES**

Gotti E.^{*}, Bazzoni E., Perego P., Bettinelli M., Zanolini A., Pavese L., Scotti A., Sansone V.A.

NeMO Clinical Centre, Neurorehabilitation Unit, University of Milan, Milan, Italy, Milan, Italy

Oral hygiene is a major determinant of oral and systemic health in patients with neuromuscular diseases and is particularly relevant for reducing pneumonia risk in ventilated individuals. Motor impairment, dysphagia, and sialorrhea significantly complicate oral care, which is therefore frequently inadequate in daily clinical practice.

To evaluate whether a structured oral hygiene program ("NeMO è ORO"), integrated within a multidisciplinary team, may reduce infections and improve overall well-being in patients with neuromuscular disorders.

Methods:

A structured oral hygiene program was developed, defining care pathways, nursing procedures, caregiver education, and best practices for adult and pediatric patients attending the NeMO Clinic in Milan. Eligibility was based on clinical observations by physicians or nurses, or on patient/caregiver request in the presence of oral or dental pain, chewing or mouth-opening difficulties, or insufficient oral hygiene strategies. Demographic and clinical data, as well as patients' and caregivers' clinical global impressions, were collected before and after program implementation.

Results:

During the first 9 months, 83 patients were enrolled and received dental care (43 ALS, 14 SMA, 25 muscular dystrophies; 77 adults and 6 pediatric patients). Longitudinal monitoring of infections and oral hygiene outcomes is ongoing.

Nurses play a pivotal role in oral health monitoring and caregiver education. A dedicated, trained multidisciplinary team is essential to ensure safe access to dental care for patients with neuromuscular diseases. The long-term impact of structured oral hygiene programs on infection rates and well-being remains to be established

OTHERS

Abstract P191 - Cod. 143205**OPTIMIZING THE USE OF CPMS 2.0 IN RARE NEUROMUSCULAR DISEASES: A MULTILEVEL IMPLEMENTATION APPROACH**

Fortunato F.^{*3}, Ferrari S.³, Neri M.³, Gualandi F.³, Atalaia A.¹, Evangelista T.², Ferlini A.³

¹ Service of Neuromyology, APHP-GH Pitié-Salpêtrière, Sorbonne Université, Paris, France, ² Neuromuscular Morphology Unit, Institute of Myology, GHU Pitié-Salpêtrière, Sorbonne Université, Paris, France, ³ Unit of Medical Genetics, Department of Medical Sciences, University of Ferrara & Unit of Medical Genetics, S. Anna University Hospital, Ferrara, Italy

E-health tools supporting telemedicine and structured knowledge exchange are a core component of the European Reference Networks (ERNs). The Clinical Patient Management System (CPMS) is a secure digital platform enabling multidisciplinary, cross-border discussion of complex clinical cases. Within the EU4H-2023-ERN-IBA program (2023–2027), ERN Euro-NMD implemented CPMS-related activities through Work Package 4 (WP4), coordinated by Sant'Anna Hospital of Ferrara.

WP4 implemented seven tasks to support the structured adoption of CPMS 2.0 across the network. Activities included two rounds of virtual trainings for clinicians and assistants in 2025, combining live demonstrations with interactive troubleshooting. Expert-moderated thematic "CPMS Days" focusing on selected neuromuscular disease groups were introduced, alongside a Pilot Reimbursement Scheme to promote participation. Platform use and user experience were evaluated through a "CPMS Periodic Monitoring Process" survey.

Limited clinical time was reported as the main barrier to CPMS adoption by 76.7% of respondents. Nevertheless, training activities and CPMS Days were widely perceived as effective facilitators of platform use. CPMS was primarily used for diagnostic clarification by 70.8% of active users. During the reporting period, 64 new users were registered, with high engagement levels: 51 users actively contributed to discussions, 38 clinical panels were opened, and 51 patients were included for cross-border consultation.

WP4 successfully implemented an integrated strategy combining capacity building, structured clinical engagement, and financial incentives. Despite persistent time constraints, user engagement supports the clinical value of CPMS. Planned initiatives include "CPMS Marathons" and a dedicated forum for newborn screening genomic data, with emphasis on variants of uncertain significance.

OTHERS

Abstract P193 - Cod. 143262**PRELIMINARY DATA ON THE SAFETY AND EFFECTIVENESS OF OMAVELOXOLONE IN FRIEDREICH'S ATAXIA: AN INITIAL ASSESSMENT WITH A THREE-MONTH FOLLOW-UP IN ADOLESCENT AND YOUNG ADULT PATIENTS ACROSS APULIAN CENTRES**

Ferrante C.^{*1}, Oliva M.C.¹, Idrissi S.², Giorelli M.², Trabacca A.¹

¹ UNIT FOR SEVERE DISABILITIES IN DEVELOPMENTAL AGE AND YOUNG ADULTS - SCIENTIFIC HOSPITAL FOR NEUROREHABILITATION - ASS. LA NOSTRA FAMIGLIA- IRCCS E. MEDEA, BRINDISI, Italy, ² OPERATIVE UNIT OF NEUROLOGY AND STROKE UNIT "DIMICCOLI" GENERAL HOSPITAL, BARLETTA, Italy

Friedreich's ataxia is a rare neurodegenerative disease. Most patients have a homozygous GAA repeat expansion in the FXN gene, resulting in a deficiency of the mitochondrial frataxin. Frataxin deficiency leads to suppression of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) antioxidant pathway, causing mitochondrial dysfunction. Omaveloxolone is a drug approved in 2023 for treating Friedreich's Ataxia. It acts as a potent Nrf2 activator reducing mitochondrial degeneration. This report evaluates its effectiveness and safety in a small case

series.

We evaluated for eligibility to Omaveloxolone three FRDA patients. All patients were eligible based on the age, (> 16), on the mFARS score (< 80), liver function, renal function (eGFR > 30 ml/min) and cardiac function (NYHA $< III$).

The mean age of recruited patients was $20,67 \pm 4,51$ years, with an M:F ratio of 1:2 with an average mFARS score 62.83 ± 15.01 .

We compared mFARS scores and haematochemicals at T0 (treatment start), T1 (10 days), and T2 (3 months). We observed symptoms stabilization based on mFARS scores.

The drug was generally well-tolerated, without symptoms. However transient increase in transaminases was noted in one (33%) patient reporting an increase of 5 times the maximum limit without signs of liver damage. In this patient it was sufficient to reduce the dose from 150 to 100 mg to normalize liver values

Our results confirm current literature regarding the drug's efficacy and tolerability. This is a small case series; larger sample and further follow-up data are needed to explore longterm effectiveness and safety of the drug.

OTHERS

Abstract P195 - Cod. 143077

PURE AUTONOMIC FAILURE: REAL-WORLD CLINICAL AND THERAPEUTIC OUTCOMES FROM AN ITALIAN COHORT

Fasano C.^{*1}, Gianoli M.², Carrozzo G.², Cani I.², Cecere A.², Domenichini S.², Provini F.², Calandra Buonauro G.², Guaraldi P.²

¹ 1. IRCCS Istituto delle Scienze Neurologiche di Bologna, University of Bologna, Bologna, Italy. 2. AOU Careggi and Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy., Firenze-Bologna, Italy, ² 1. IRCCS Istituto delle Scienze Neurologiche di Bologna, University of Bologna, Bologna, Italy, Bologna, Italy

Pure autonomic failure (PAF) is a rare neurodegenerative disorder of the peripheral autonomic nervous system, primarily characterized by orthostatic hypotension (OH) and associated with other manifestations of autonomic dysfunction. Real world data on disease course and especially regarding therapeutic effectiveness in PAF remain limited.

We retrospectively evaluated 31 patients diagnosed with PAF and referred to the Autonomic Laboratory of the IRCCS Istituto delle Scienze Neurologiche of Bologna. Demographic, clinical and therapeutic data were collected, including treatment outcomes up to the last available follow-up.

Among the 31 patients, 25 are men (80%) and 6 women (20%); median follow up duration 8 years (± 2). All patients presented with orthostatic hypotension, associated with additional autonomic symptoms; among these erectile (67%) and urinary tract dysfunctions (39%) were the most frequent. Ganglionic acetylcholine receptor (gAChR) antibodies were detected in one patient only. Sixteen patients (53%) were treated with droxidopa (DOPS), at a mean daily dose of 800 mg (± 614.3), either as monotherapy or in combination with fludrocortisone or midodrine. Symptomatic improvement was observed in 21 patients (70%), by means of improved orthostatic tolerance and reduction in syncopal episodes. Treatment was discontinued

due to lack of efficacy in 6 cases and adverse effects were reported in 4 patients.

PAF is a rare and under-recognized disorder. In this cohort, we report a real-world therapeutic management data showing encouraging effectiveness and a favourable safety profile. To our knowledge, this represents the first Italian cohort providing detailed therapeutic outcomes in PAF.

OTHERS

Abstract P197 - Cod. 142699

SERUM GALECTIN-3 AS A BIOMARKER IN ACUTE INFLAMMATORY POLYRADICULONEUROPATHIES: A COHORT STUDY

Siconolfi G.^{*1}, Primiano G.², Vitali F.³, Sciarrone M.A.³, Guglielmino V.¹, Ciasca G.⁴, Basile U.⁵, Luigetti M.⁶

¹ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, 00168, Rome, Italy., Rome, Italy, Italy, ² Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, 00168, Rome, Italy. guidoalelessandro.primiano@policlinicogemelli.it, rome, Italy, ³ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, 00168, Rome, Italy, Roma, Italy, ⁴ Sezione di Fisica, Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, 00168, Rome, Italy., Roma, Italy, ⁵ Dipartimento di Patologia Clinica, Ospedale Santa Maria Goretti, A.U.S.L. Latina, 04100, Latina, Italy., Latina, Italy, ⁶ Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168, Rome, Italy., Roma, Italy

Guillain-Barré Syndrome (GBS) refers to acute inflammatory polyradiculopathies characterized by a diffuse inflammatory attack on the peripheral nervous system. In this study, we propose galectin-3 (Gal-3), a novel serum molecule identified expressed by Schwann cells and macrophages, as a potential biomarker in patients with GBS.

Serum levels of Gal-3 and neurofilament light chain (NfL) were measured using the immunoassay on the Ella platform (ProteinSimple, San Jose, CA, USA) in serum samples from a cohort of patients with GBS (n = 19) and in a validation cohort of healthy control subjects (n = 13).

Gal-3 levels were significantly higher in patients with GBS (median: 7041 pg/mL; IQR: 5576-8561) compared to healthy controls (median: 5030 pg/mL; IQR: 3877-5998; $p < 0.05$). Within the GBS cohort, Gal-3 levels were significantly elevated in patients with the axonal variant compared to those with AIDP variant (median: 8561 pg/mL vs. median: 5998 pg/mL, $p < 0.05$). In multivariate logistic regression, log-transformed Gal-3 remained significantly associated with the axonal variant of GBS after adjustment for age at sampling, diarrhea, GBS Disability Score at admission, and NfL. In ROC curve analysis, Gal-3 demonstrated good discriminatory performance between axonal GBS and AIDP (AUC = 0.84), outperforming NfL (AUC = 0.76). Gal-3 threshold of 6457.5 pg/mL was identified, yielding 100% sensitivity for distinguishing axonal GBS.

In our cohort, Gal-3 was associated with both diagnostic and prognostic features in patients with GBS. These findings suggest that Gal-3 may serve as a potential biomarker for differentiating axonal subtypes within the GBS spectrum.

OTHERS

Abstract P199 - Cod. 143453

SYMPTOMATIC MUSCULAR SARCOIDOSIS: CLINICAL HETEROGENEITY AND TREATMENT RESPONSE IN A MULTICENTER CASE SERIES

Colacicco G.*¹, D'Amico L.², Velardo D.³, Ripolone M.³, Laurini C.⁴, Vanoli F.⁵, Maggi L.⁵, Previtali S.⁴, Corti S.³, Comi G.P.³, Sansone V.A.¹

¹ The NeMO Clinical Center Milan, Neurorehabilitation Unit, University of Milan, Italy, Milano, Italy, ² Department of Neurology, University of Milan, Italy, Milano, Italy, ³ Neuromuscular and Rare Disease Unit, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Milan, Italy, Milano, Italy, ⁴ Neuromuscular Repair Unit, IRCCS San Raffaele Scientific Institute, Milan, 20132, Italy, Milano, Italy, ⁵ Neuroimmunology and Neuromuscular Diseases Unit, Fondazione IRCCS Istituto Neurologico C. Besta, Milan, Italy, Milano, Italy

Symptomatic muscular sarcoidosis is rare and can mimic other inflammatory or genetic myopathies. In some patients, muscle disease precedes or reveals otherwise clinically silent systemic sarcoidosis. We conducted a retrospective multicenter case series across four neuromuscular units in Milan, Italy. Patients were included when sarcoidosis was supported clinically and confirmed by muscle biopsy showing non-caseating granulomas. We recorded demographics, presenting symptoms, weakness distribution, dysphagia, creatine kinase (CK), extramuscular involvement, key imaging (muscle MRI and/or FDG-PET/CT when available), treatment, and clinical and metabolic responses.

Five patients (three women) were identified over five years. Age at symptom onset ranged from 56–73 years, and age at neuromuscular evaluation from 63–76 years. Proximal weakness was present at onset in 4/5 cases; in one patient it was the first manifestation leading to diagnosis of previously unrecognized systemic sarcoidosis. Dysphagia occurred in 2/5. CK ranged from 81 to 560 U/L. Extramuscular involvement was heterogeneous, most commonly lymph nodes and/or the respiratory tract. Muscle MRI revealed marked atrophy with selective fatty replacement. FDG-PET/CT demonstrated diffuse muscular and nodal hypermetabolism. Glucocorticoids produced overall systemic improvement and marked metabolic response on PET/CT, whereas gains in strength and function were variable and often incomplete.

Symptomatic muscular sarcoidosis shows heterogeneous presentations and may be the first clue to systemic disease. Muscle biopsy remains the diagnostic cornerstone, while MRI and/or FDG-PET/CT help define extent and monitor activity. The frequent dissociation between metabolic/systemic response and persistent functional disability supports early recognition and treatment to limit irreversible muscle damage at presentation.

OTHERS

Abstract P201 - Cod. 142945

TELEMEDICINE IN THE NEUROMUSCULAR

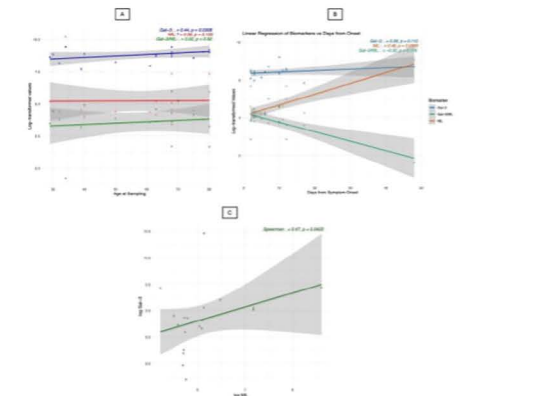


Fig. 3 Linear regression plots of Gal-3, Gal-3/NIL, and NIL, with days from symptom onset, age at sampling and age at sampling. Linear regression plots showing significant correlations between Gal-3 levels and A age at symptom onset, B days from symptom onset, and C log transformed NIL concentrations. Spearman correlation coefficients (rho) and corresponding p-values are indicated above each panel. In GBS patients, Gal-3 levels were positively correlated with age and NIL levels, whereas no significant correlations were observed with other clinical measures, including GBS-DSS, disease duration, mEGFR, or mEGFR at admission.

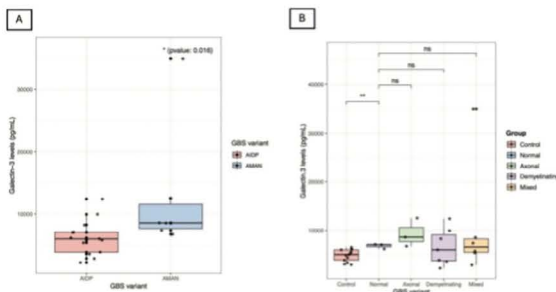


Fig. 2 Boxplot of serum levels of Gal-3 in subgroup based on NCS findings firstly in axonal GBS variant (AMAN or AMSAN) and AIDP patient (A) and in relation to electrophysiological findings (B). A shows a double box plot of Gal-3 levels in AIDP and axonal GBS patients. Median Gal-3 levels were significantly higher in axonal patients compared to AIDP patients, as determined by the Wilcoxon rank sum-test, with the p-value indicated in the top-left corner. B illustrates Gal-3 levels stratified by admission electrophysiological characteristics (normal, axonal, demyelinating, and mixed). Significant differences assessed using the Kruskal-Wallis test followed by post hoc Dunn's test, are indicated by asterisks and connecting lines, while non-significant differences are marked with lines and 'ns'. Notably, all patient subgroups showed significantly higher median Gal-3 levels compared to control subjects.

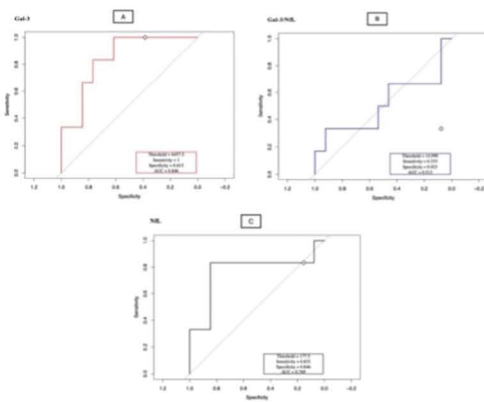


Fig. 4 Discriminatory performance of Galactin-3 and Gal-3/NIL. Ratio between Axonal and AIDP GBS patients. ROC curves demonstrating the diagnostic performance of serum Gal-3 levels (A), Gal-3/NIL ratio (B), and serum NIL levels (C) in distinguishing the axonal variant (AMAN or AMSAN) from AIDP. Threshold values, along with their corresponding sensitivity, specificity, and AUC are reported in the boxes above each panel.

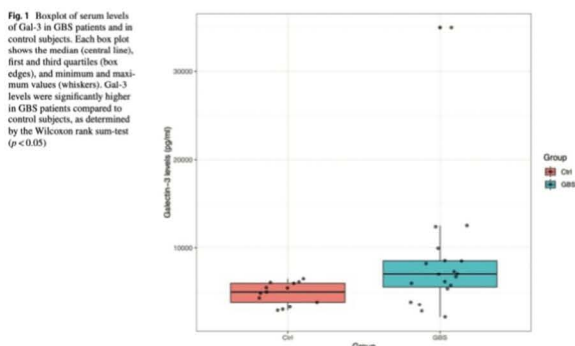


Fig. 1 Boxplot of serum levels of Gal-3 in GBS patients and in control subjects. Each box plot shows the median (central line), first and third quartiles (box edges), and minimum and maximum values (whiskers). Gal-3 levels were significantly higher in GBS patients compared to control subjects, as determined by the Wilcoxon rank sum-test ($p < 0.05$).

DISEASE CLINIC AS A TOOL FOR PATIENT STRATIFICATION

D"Amico F.*, Cirafisi G., Lo Mauro E., Rini N., Alonge P., Lima S.M., Quartetti U., Portera V., Messina C., Brighina F., Di Stefano V.
Department of Biomedicine, Neuroscience and Advanced Diagnostics (BiND), University of Palermo, 90127, Palermo, Italy

The role of telemedicine is widely debated in the healthcare field. The aim of this study is to evaluate the effectiveness of telemedicine in reducing waiting lists and adjusting patient urgency to visit timing, as well as maximizing clinic resources and meeting patient compliance. The main tool used was the teleconsultation: an exploratory virtual meeting without clinical examination, in which further diagnostic tests can be recommended.

All patients who had a first-time appointment between October 2025 and March 2026 at the "Rare Neuromuscular Disease Diagnosis and Treatment Clinic" of the Paolo Giaccone Polyclinic in Palermo were contacted to assess adherence to the telemedicine project, followed by a remote teleconsultation. The outcome of the teleconsultation could be: improper visit, maintaining the original booking date, anticipating the visit, the teleconsultation was considered exhaustive, and remote telehealth visit was conducted.

Of the 74 patients contacted, 28 actually performed the first teleconsultation (37%). The results of the teleconsultations were: 5 improper visits (17%), 15 maintenance of the original reservation (53%), 5 early visits as urgent (17%), 2 exhaustive teleconsultations, 1 telehealth visit. As a main result, the urgent visit anticipation has allowed to reduce patients' waiting times: visits were brought forward by an average of 60 days.

Our experience confirms that teleconsultation can be an important tool for patient stratification and proper timing of visits. Furthermore, a comparative study can evaluate its use both in initial visits and in follow-up visits of patients already known to the clinic.

OTHERS

Abstract P203 - Cod. 143367

TOWARDS THE DEVELOPMENT OF A TRANSITION PATHWAY IN NEUROMUSCULAR DISORDERS

Patanella A.K.*¹, Primiano G.², Catteruccia M.³, Diodato D.³, Tosi M.³, Deodato F.³, Sancricca C.⁴, D"Amico A.³

¹ Centro NeMo Armida Barelli, Rome, Italy, ² Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ³ Bambino Gesù, Children's Hospital IRCCS, Rome, Italy, ⁴ Fondazione UILDM Lazio Onlus, Rome, Italy

The transition from pediatric to adult services is a pivotal phase in the care of patients with neuromuscular disorders (NMD) and is frequently associated with an increased risk of discontinuity of care, loss to follow-up, and suboptimal clinical management.

To describe the development of a transition pathway from Bambino Gesù Children's Hospital (pediatric referral center) to the adult neuromuscular centers Fondazione Policlinico Universitario Agostino Gemelli and Centro NeMo Armida Barelli, and to identify its strengths

and limitations and assess patient and family satisfaction.

Methods

A shared transition pathway was developed through close collaboration between pediatric and adult neurologists. Transition planning was initiated at age 16, with patients and families receiving structured information on the transition process, the adult centers' expertise, and continuity-of-care arrangements. Written consent was obtained for the transfer of sensitive medical records and contact details.

From 2019 to the present, 35 patients with spinal muscular atrophy, muscular dystrophies, hereditary neuropathies, channelopathies, and metabolic, congenital, and mitochondrial myopathies completed the transition pathway. Continuity of follow-up was maintained in all cases throughout the transition period, with no losses to follow-up. At present, joint transition visit involving both teams, has not yet been implemented. Preliminary findings suggest high satisfaction among patients and their families

Conclusions

Implementation of a structured transition pathway is feasible. Our experience underscores the importance of coordinated, patient-centered care in maintaining continuity for individuals with NMD. Ongoing and future evaluation will focus on patient-reported satisfaction and the pathway's long-term outcomes.

OTHERS

Abstract P205 - Cod. 143291

WHEN DROPPED HEAD IS NOT MOTOR NEURON DISEASE: ANTISYNTHEASE SYNDROME MIMICKING NEUROGENIC PATHOLOGY

Musacco A.*, Raia M., Russo M., Messina S., Rodolico C.

Dipartimento di medicina clinica e sperimentale, Università degli studi di Messina,, Messina, Italy

Dropped head syndrome is an unusual expression of axial muscle weakness which challenges physicians in discerning between myopathies, motor neuron disease, myasthenia gravis and systemic syndromes.

We introduce the case of a 76- year-old male with right eye ptosis since the age of 20 and a worsening course in the past years of dropped head and shoulder girdle weakness.

Clinical examination showed diffuse muscular atrophy and some fasciculations raising the suspect of motor neuron disease. Yet electromyography (EMG) showed predominantly myopathic MUPs with mild denervation; both repetitive nerve stimulation and CMAP (6mV) were normal, excluding congenital myasthenic syndromes. Paraneoplastic markers were negative as well as autoantibodies against Ach receptor and anti- MUSK. Muscle MRI showed hyperintensity of rectus femori in STIR scans and severe hypotrophy of multifidus, cervical and dorsal paraspinal muscles. Muscle biopsy results are still pending. Although creatine kinase (CK) was within the upper limits of normal range, myositis-specific autoantibody positivity Jo1 together with Chest

Computed Tomography (CT scan) exhibiting interstitial lung disease (ILD) led to a diagnosis of Antisynthetase syndrome (ASS).

This case highlights how subtle dropped head can be as a symptom, hampering the diagnostic process. Even if rare, diseases such as ASS should be considered in order to prevent a delayed diagnosis.

OTHERS

Abstract P207 - Cod. 143037

“MOTOR REHABILITATION IN MUSCULAR DYSTROPHIES FROM HOSPITAL TO HOME: A PILOT PROJECT”

Diella E., Falivene A., Ghezzi C.*, Delle Fave M., Cima R., D’Angelo M.G.

Scientific Institute IRCCS Eugenio Medea, Bosisio Parini, Italy

Regular, moderate-intensity, patient-tailored exercise is safe in muscular dystrophies (MDs) and potentially slows down disease progression. Home and tele-rehabilitation have emerged as feasible and sustainable alternatives to conventional physical therapy to maintain muscle strength and functional status and could be valuable tools to drive motor rehabilitation from hospital to home.

The aim of our study is to evaluate feasibility and effects of a 6-month home-based motor rehabilitation program in patients affected by MDs. 6 individuals (47.32 ± 10.3 y/o, 5 males) affected by muscular dystrophy (2 FSHD, 2 BMD, 1 LGMD-R2/2B, 1 EDMD2) underwent 6 months of home training scheduled 3 times per week with 1 session per week carried out in tele-rehabilitation through the Khymeia Home-Kit system. Home rehabilitative sessions consisted of a combination of tailored aerobic and strength submaximal training and muscle flexibility exercises. Motor function, fatigability and quality of life were assessed pre-training, after 3 months and after 6 months of training. Considering the small sample size, no formal statistical analyses were performed to assess short and long-term effects of our training program. Data were analyzed within a descriptive case-series framework.

Preliminary results show that participants who adhered strictly to the program achieved goals in terms of increased endurance, fatigue reduction and improved well-being.

Our home rehabilitation program, although quite demanding to sustain, if followed consistently, is feasible and effective allowing the achievement of significant results. Therefore, home and tele-rehabilitation seem useful to promote an “active lifestyle” and prevent “disuse” atrophy.

OTHERS

Abstract P209 - Cod. 143001

“WEARABLE SENSORS TO MONITOR NEUROMUSCULAR PATIENTS IN REAL WORLD ENVIRONMENT”

Diella E.*¹, Storm F.A.¹, Molteni L.E.¹, Delle Fave M.¹, Ghezzi C.¹, Meola G.², Biffi E.¹, D’Angelo M.G.¹

¹ *Scientific Institute IRCCS Eugenio Medea, Bosisio Parini, Italy*, ² *University of Milan, Milano, Italy*

Wearable sensors are becoming increasingly popular for remote monitoring of patient’s motor function in real world offering information on patient’s daily physical activity.

Our aim is to collect and profile physical activity data in daily living conditions with the purpose of defining digital “real world biomarkers” available as complementary endpoints to traditional outcome measures in future assessments. We collected data of 10 patients affected by muscular dystrophy (7 Steinert, 1 FSHD, 1 BMD, 1 LGMD-R2/2B) and 3 healthy age-matched controls. Home monitoring was performed wearing consecutively for 7-days a single lumbar-mounted inertial measurement unit (Dynaport 7, McRoberts) to extract physical activity data in real world environment. Digital mobility outcomes (i.e. active/inactive time, type of activity, number of steps) were obtained and analyzed for each subject.

Preliminary results show significant differences between patients and controls in the percentages of physical activity performed weekly and in the number of steps taken daily. These data correlate with the subject’s performance at the 6-Minute Walk Test.

Evaluating and monitoring patients with muscular dystrophy in ecologic setting could significantly impact on patient care promoting an active life style. Digital “real world biomarkers” could potentially be exploited as complementary endpoints in future clinical trials and to predict disease trajectories using advanced algorithms including AI.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P211 - Cod. 143279

NEUROPSYCHOLOGICAL PROFILE TRAJECTORIES IN SMA PEDIATRIC POPULATION: A SINGLE CENTRE STUDY

Scarpini G.*³, Fabbri M.¹, Gruppioni B.¹, Morales E.¹, Pizzoli C.¹, Bonazzi S.¹, Giannotta M.³, Trentin F.³, Cordelli D.M.², Pini A.³

¹ *Centro Regionale Disabilità Linguistiche e Cognitive, UOC Neuropsichiatria dell’Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy*, ² *Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università di Bologna, Bologna, Italy*, ³ *UOS Malattie Neuromuscolari dell’Età Evolutiva, UOC Neuropsichiatria dell’Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy*

The clinical features and progression of SMA are well documented, whereas less is known about affected children’s cognitive and communication skills. Polido et al. (2019) conducted a systematic review reporting heterogeneous cognitive outcomes in SMA patients, with many patients scoring within the normal IQ range despite some deficits. Understanding their cognitive profile is essential to support communication, social skills, learning, and problem-solving from early childhood.

Our center assessed 15 SMA patients aged 18 months to 11 years (types I, II, and III), including sitters and walkers, all receiving a disease modifying treatment. Nine patients underwent longitudinal evaluation. Neuropsychological assessments were conducted using age-appropriate tools (e.g., Bayley III, Wechsler, Leiter 3, NEPSY-II), while communication skills were evaluated with standardized tools (e.g., PVB-MacArthur, PVCL, PING). The goal was to characterize their neuropsychological profile to facilitate tailored interventions.

We detected poorer performance in visual-motor and visual-constructive tasks. Although many had normal IQ, specific cognitive domains such as attention and executive functions could be affected, aligning with recent studies (Masson 2021). In our cohort, only one patient presented with intellectual disability and communication impairment. Difficulties in language development were observed in different areas, such as speech, semantic control and lexical retrieval. Early exposure to gestures enhances joint attention in terms of visual-motor and proprioceptive integration, while the use of gestures in communication supports social interaction, encouraging symbolic and semantic development. Future research should explore the impact of early pharmacological treatment since neonatal age on cognitive developmental trajectories.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P213 - Cod. 142793

A DE NOVO DYNC1H1 MUTATION IN SMA-LED TYPE 1: THE IMPORTANCE OF ADVANCED GENETIC TESTING

Vallefuoco F.¹, Zoppi D.¹, Russo A.¹, De Maria M.¹, Russo R.¹, Boemia V.¹, Esposito G.², Ruggiero L.¹

¹ *Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples, "Federico II", Naples, Italy., Napoli, Italy,*
² *CEINGE-Biotecnologie Avanzate Franco Salvatore, Naples, Italy., Napoli, Italy*

Background: Most Spinal Muscular Atrophy (SMA) cases involve 5q13 (SMN1) deletions.

However, mutations in the DYNC1H1 gene cause an autosomal dominant form known as SMA-LED (Spinal Muscular Atrophy with Lower Extremity Dominance), primarily affecting the lower limbs.

We describe a female patient followed at our Neuromuscular Disease Center. The diagnostic workup included neurological evaluation, electrophysiological studies, muscle biopsy, MLPA for SMN1/

SMN2, a Next-Generation Sequencing (NGS) neuromuscular panel, and Whole Exome Sequencing (WES).

Results: The patient had surgery for congenital clubfoot and showed delayed motor milestones (walking at 30 months). Since age six, she exhibited progressive gait difficulties, lower limb weakness (quadriceps femoris), and Achilles tendon retraction. CPK levels were normal.

Neurophysiology showed diffuse neurogenic involvement; muscle biopsy revealed marked fibrous replacement. While MLPA showed a homozygous SMN2 deletion and NGS identified a single heterozygous SMN1 variant, these findings were inconclusive for recessive SMA. Subsequent WES identified a de novo heterozygous pathogenic variant in DYNC1H1 (c.2327C>T; p.Pro776Leu).

Conclusions: The clinical profile was consistent with a motor neuron disorder predominantly affecting the lower limbs. This case emphasizes that clinicians should not settle for partially matching genetic results. Although SMA-LED is rare, it must be considered in the differential diagnosis of childhood motor neuron diseases, utilizing advanced tools like WES to clarify complex phenotypes.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P215 - Cod. 143405

ASSESSMENT OF ACTIVITIES OF DAILY LIVING (ADL) IN SPINAL MUSCULAR ATROPHY (SMA) PATIENTS TREATED WITH DISEASE-MODIFYING THERAPY: CASE SERIES

Oliva M.C.^{*}, Ferrante C., Morleo G., Distante F., Maniglio J., Vespino T.C., Trabacca A.

UNIT FOR SEVERE DISABILITIES IN DEVELOPMENTAL AGE AND YOUNG ADULT - SCIENTIFIC HOSPITAL FOR NEUROREHABILITATION - ASS. LA NOSTRA FAMIGLIA - IRCCS E. MEDEA, Brindisi, Italy

The most frequently reported ADL limitations in SMA patients included mobility. Upper limb function and instrumental ADLs were

	Pazient	Functional Status	WeeFIM	SMAIS ULM
COHORT 1	1	No Sitter	INCREASE	INCREASE
	2	No Sitter	INCREASE	INCREASE
	3	No Sitter	INCREASE	INCREASE
	4	Sitter	INCREASE	INCREASE
	5	Walker	INCREASE	INCREASE
COHORT 2	6	No Sitter	FLOOR	FLOOR
	7	No Sitter	FLOOR	FLOOR
	8	Sitter	INCREASE	INCREASE
	9	Sitter	FLOOR	INCREASE
	10	Walker	INCREASE	CEILING
	11	Walker	CEILING	CEILING

Table 1: Table shows improvements, floor or ceiling effects across different functional subgroups in the WeeFIM and SMAIS - ULM questionnaire.

less frequently assessed but emerged as important in maintaining autonomy, particularly in adolescents.

The aim of the study is to show any improvements in autonomy in daily living activities in treated SMA patients.

A total of 11 symptomatic patients, divided into 2 cohorts, were evaluated. Cohort 1 included 5 individuals aged 2 – 3 years of which 3 non-sitters (SMA I), 1 sitter (SMA II) and 1 walker (SMA III) diagnosed in disease-modifying treatment era.

Cohort 2 comprised 6 individuals aged 6–16 years (mean age 11,7 (3,68)) of which 2 non-sitters (1 SMA I and 1 SMA II), 2 sitters (SMA II) and 2 walkers (SMA III) diagnosed before 2017.

Mean duration of disease at the start of treatment was respectively 3,4 (2,15) months and 10 (3,41) years.

The WeeFIM and the SMAIS – ULM were performed in all patients at the beginning of therapy (T0) and after 12 months (T1).

The changes in measurements performed at T1 compared to T0 are summarized in Table 1.

Attention to self-care and fine-motor ADLs as to gross-motor mobility will be essential for translating therapeutic advances into real-world independence.

WeeFIM and SMAIS - ULM analyze different aspects of autonomy in everyday life. Functional status and early treatment are important for improving or maintaining independence in ADL. New tools are needed to assess improvements in ADL, especially in the most severely ill patients.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P217 - Cod. 143395

BMI AND MOTOR FUNCTION IN A POPULATION OF ITALIAN PEDIATRIC AND ADULT PATIENTS WITH SMA: IS THERE A CORRELATION?

Briganti E.^{*1}, Scarpini G.², Not R.², Giannotta M.², Trentin F.², Polizzi S.³, Merlotti A.⁴, Remondini D.⁴, Cordelli D.M.¹, Coratti G.⁵, Agosto C.⁶, Bitetti I.⁷, Brolatti N.⁸, Bruno I.⁹, Coccia M.¹⁰, Filosto M.¹¹, Gagliardi D.¹², Garibaldi M.¹³, Maggi L.¹⁴, Messina S.¹⁵, Sframeli M.¹⁵, Mongini T.E.¹⁶, Nigro V.¹⁷, Pegoraro E.¹⁸, Ricci F.S.¹⁹, Ruggiero L.²⁰, Sansone V.²¹, Albamonte E.²¹, Siciliano G.²², Ticci C.²³, Trabacca A.²⁴, Vacchiano V.²⁵, Liguori R.²⁵, Verriello L.²⁶, Pessa M.E.²⁶, Mercuri E.M.⁵, Pini A.²

¹ Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy, ² Pediatric Neuromuscular Unit, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ Data Science and Bioinformatics Laboratory, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ⁴ Department of Physics and Astronomy (DIFA), University of Bologna, Bologna, Italy, ⁵ Pediatric Neurology, Università Cattolica del Sacro Cuore, Rome, Italy, ⁶ Department of Women's and Children's Health, University of Padua, Padua, Italy, ⁷ Pediatric Neurology, Santobono-Pausilipon Children's Hospital, Neurology Unit, Naples, Italy, ⁸ Center of Translational and Experimental Myology, and Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genova, IRCCS Istituto Giannina Gaslini, Genoa, Italy, ⁹ Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, ¹⁰ Department of Neurological Sciences, AOU Ospedali Riuniti

di Ancona, Ancona, Italy, ¹¹ Department of Clinical and Experimental Sciences, University of Brescia (Italy), NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ¹² Pediatric Neurology Unit, Pediatric Hospital Giovanni XXIII, Bari, Italy, ¹³ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ¹⁴ Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ¹⁵ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ¹⁶ Neuromuscular Unit, Department of Neurosciences, University of Turin, Turin, Italy, ¹⁷ Medical Genetics and Cardiomyology Unit, Department of Precision Medicine, Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy, ¹⁸ Neurology Unit, Azienda Ospedale Padova, Padua, Italy, ¹⁹ Complex Structure of Child and Adolescent Neuropsychiatry, A.O. Ospedale Infantile Regina Margherita-S. Anna, University of Turin, Turin, Italy, ²⁰ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy, ²¹ The NeMO Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Milan, Italy, ²² Neurology Unit, AOU Pisana (Department of Clinical and Experimental Medicine), Pisa, Italy, ²³ Metabolic Unit, A. Meyer Children's Hospital, Florence, Italy, ²⁴ Developmental Neurology and Neurorehabilitation, Unit for Severe disabilities in Developmental Age and Young Adults, IRCCS "E. Medea", Brindisi, Italy, ²⁵ UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ²⁶ Neurology Unit, Department of Neurosciences, University Hospital Santa Maria della Misericordia, Udine, Italy

The aim of this study is to explore a possible longitudinal correlation between BMI (Body Mass Index) and functional motor performances in pediatric and adult treated and untreated patients with 5q-SMA (Spinal Muscular Atrophy linked to chromosome 5q).

A total of 190 symptomatic patients included in the ITASMAC Registry were enrolled in this retrospective cohort study (13 SMA 1, 95 SMA 2, 82 SMA 3): 148 were pediatric patients (age ≥ 6 and < 20 years), with 862 total measurements; 42 were adults (age ≥ 20 years), with 205 measurements. In this sample, we analyzed variations in BMI and functional motor scales (HFMSE = Hammersmith Functional Motor Scale Expanded for SMA and 6MWT = 6-Minute Walk Test) for each patient.

We observed that, both in pediatric and adult patients, each unit increase in BMI (over time and within subjects) is associated with a significant decrease in the 6MTW total distance and in the HFMSE total score: we also have seen that this trend is stronger in the HFMSE weight-bearing items. These findings are even more evident in adults. Overall, the present results suggest poorer functional motor performance in patients with a higher BMI, above all in adolescent and adult subjects. Further studies are needed to explore the impact of body composition (particularly overweight and underweight) on motor function, in patients with a neuromuscular disease such as SMA. This would help to better evaluate dietary approaches and clinical trends over time, also in relation to disease modifies treatment.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P219 - Cod. 143490

CAN WE INTEGRATE THE SMA RESPONSE TO THERAPIES ASSESSMENT? LOOKING FOR EASY-TO-USE TOOLS

Carraro L.¹, Conti C.^{*1}, Baldini E.², Khalil S.¹, Pratile D.C.¹, Gardani A.³, Berardinelli A.³

¹ Università degli studi di Pavia, Department of Brain and Behavioral Sciences, Pavia, Italy, ² IRCCS Fondazione Mondino, National Neurological Institute, Department of Cardiology, Pavia, Italy, ³ IRCCS Fondazione Mondino, National Neurological Institute, Department of Child Neurology and Psychiatry, Pavia, Italy

The introduction of DMTs has reshaped the clinical course of SMA, revealing limitations of conventional motor scales. Although reliable and widely used, they may not capture subtle qualitative changes as fasciculations, tremor, fatigue, and patient-perceived autonomy gains. Therefore, additional easy-to-use tools to detect these minor changes are needed.

Electrophysiological measures, such as cMAP, were introduced to detect early disease onset in apparently asymptomatic children diagnosed through NBS. ECG in SMA is characterized by regular spike potentials (39–48 cycles/sec) on the isoelectric line, interpreted as fasciculations from denervated muscles.

We explored whether other electrophysiological measures could complement standard assessment, in particular if fasciculations at ECG could change secondarily to DMTs.

Eleven patients (seven SMA 3, four SMA 2) underwent serial follow-up evaluations including ECG recordings. We analyzed fasciculations using mixed-effects models and systematically reviewed and categorized into predefined Features and Domains clinical notes.

Over extended follow-up, fasciculation amplitude decreased early and remained lower; fasciculation number significantly reduced only at later time points. In some cases, fasciculations were no longer visible on later recordings. Changes were independent of SMA type, sex, and SMN2 copy number.

Clinical notes reported improvements in autonomy, strength, endurance, and balance. SMA 2 patients predominantly showed axial and postural gains while SMA 3 patients gait and upper-limb function improvements. Endurance benefits emerged earlier than autonomy gains.

These exploratory findings suggest that longitudinal ECG assessment combined with systematic clinical analysis can capture meaningful changes not fully reflected by standard motor scales, supporting a multidimensional approach to SMA evaluation in the DMT era.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P221 - Cod. 142964

COGNITION, QUALITY OF LIFE, AND PSYCHOLOGICAL FEATURES IN A SINGLE-CENTRE COHORT OF ADULTS WITH SPINAL MUSCULAR ATROPHY

Gadaleta G.^{*1}, Batti V.², Urbano G.¹, Maccarrone G.¹, Vercelli L.¹, Rolle E.¹, Leopizzi E.¹, Boschi S.¹, Geminiani G.C.³, Mongini T.¹

¹ Neuromuscular Unit, Department of Neurosciences "Rita Levi Montalcini", University of Turin, Turin, Italy, ² Clinical Psychology Unit, A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy, ³ Department of Psychology, University of Turin, Turin, Italy

In adults with spinal muscular atrophy (SMA), motor impairment is

the defining clinical feature, while the extent of cognitive and psychosocial involvement remains unclear. Evidence in adult SMA is limited and heterogeneous, with cognitive assessment potentially confounded by the use of screening tools that rely on motor output.

To explore cognition, quality of life, and psychological features in adults with SMA type 2 and 3 using a single, concurrent multidomain assessment designed to minimise motor demands and fatigue, and to examine the relationship between cognitive measures, patient-reported outcomes, and motor status.

Fifteen adults were evaluated (SMA2 n = 4, SMA3 n = 11). Global cognitive performance was largely preserved. Compared with SMA3, individuals with SMA2 showed lower MoCA scores driven by motor-dependent items. In contrast, Digit Span Backward, a verbally administered and motor-independent working-memory task, was lower in SMA2, suggesting a potential selective executive vulnerability not explained by muscle weakness alone. SF-36 Physical Functioning aligned with motor severity, whereas role and mental health domains showed a trend toward higher scores in SMA2 despite greater physical impairment. SCL-90-R scores were mostly within the normal range, with mild positive associations between higher motor function and phobic anxiety/global distress.

In our cohort of adults with SMA2–3, cognition appeared largely preserved, with motor-dependent cognitive measures requiring cautious interpretation. In this context, Digit Span Backward may provide motor-independent information that complements global screening. Patient-reported quality of life (SF-36) and psychological measures (SCL-90-R) may capture unexpected psychosocial aspects not evident from motor status and support clinical screening/referral to psychological care.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P223 - Cod. 143449

DEVOTE PART C AND ONWARD INTEGRATED RESULTS: HIGHER DOSES OF NUSINERSEN IN NUSINERSEN-EXPERIENCED PARTICIPANTS WITH SPINAL MUSCULAR ATROPHY (SMA)

Mercuri E.M.^{*1}, Finkel R.², Crawford T.³, Day J.W.⁴, Montes J.⁵, Garcia Romero M.D.M.⁶, Sumner C.J.⁷, Paradis A.D.⁸, Sun P.⁸, Foster R.⁹, Gambino G.⁹, Littauer R.⁸, Fradette S.⁸, Farewell R.⁸

¹ Pediatric Neurology Unit, Catholic University, Rome, Italy, ² Center for Experimental Neurotherapeutics, St Jude Children's Research Hospital, Memphis, TN, USA, United States of America, ³ Hopkins University School of Medicine, Baltimore, MD, United States of America, ⁴ Department of Neurology, Stanford University School of Medicine, Palo Alto, CA, United States of America, ⁵ Columbia University Irving Medical Center, New York, NY, United States of America, ⁶ Hospital La Paz, Madrid, Spain, ⁷ Johns Hopkins University School of Medicine, Baltimore, MD, United States of America, ⁸ Biogen, Cambridge, MA, United States of America, ⁹ Biogen, Maidenhead, United Kingdom

DEVOTE (NCT04089566; 3-part, Phase 2/3 trial) and ONWARD (NCT04729907; Phase 3 open-label long-term extension) evaluate higher-dose nusinersen in participants with SMA.

DEVOTE Part C (open-label) enrolled 40 participants (aged 4–65 years) with infantile or later-onset SMA who transitioned to higher-

dose nusinersen after ≥ 1 year on 12/12 mg. Participants received one 50 mg loading dose four months ± 14 days after their last 12 mg dose, followed by two 28 mg maintenance doses on Days 121 and 241. Safety was the primary endpoint.

Participant demographics were heterogeneous by design, with broad baseline Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) scores. Adverse events occurred in 37/40 (92.5%) participants: mild or moderate in 32/40 (80%), severe in 5/40 (12.5%). Baseline plasma neurofilament light chain (NfL) levels were within the range of neurologically healthy individuals and remained low after transitioning to 50/28 mg. Most participants had improvements on HFMSE, RULM, and/or Clinical Global Impression–Change (CGI-C) (assessed by investigator/caregiver) after transitioning.

50/28 mg nusinersen was generally well tolerated, with adverse events broadly consistent with 12/12 mg. Some improvements exceeded expectations for individuals having previously received 12/12 mg nusinersen for a median of 3.9 years. These data support transition to 50/28 mg.

At interim cutoff, ONWARD Part C enrolled 39 participants. The primary endpoint is safety and tolerability, and 50/28 mg was generally well tolerated. Pre-dose evaluations of ONWARD day 1 show HFMSE and RULM improvements/stabilization across subgroups. Longer-term results will be debuted.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P225 - Cod. 142971

EFFECTIVENESS OF RISDIPLAM ON UPPER LIMB MOTOR FUNCTION IN ADULTS: A REAL-WORLD EXPLORATORY META-ANALYSIS

Alonge P.^{*1}, Gadaleta G.², Urbano G.², Rini N.¹, Di Stefano V.¹, Crescimanno G.³, Lupica A.¹, Brighina F.¹

¹ Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy, ² Neuromuscular Unit, Department of Neurosciences “Rita Levi Montalcini”, University of Turin, Torino, Italy, ³ Institute for Biomedical Research and Innovation (IRIB), National Research Council (CNR), Palermo, Italy

Risdiplam is an oral SMN2 splicing modifier with proven efficacy in spinal muscular atrophy (SMA), but real-world evidence in adult patients is still limited.

To evaluate the effectiveness of risdiplam on upper limb motor function, as measured by the Revised Upper Limb Module (RULM), in adults with 5q-associated SMA.

A meta-analysis was conducted through a systematic review using the search terms “adult” and “risdiplam”. Nine observational studies published between 2023 and 2025 were included, comprising 132 adults with 5q-associated SMA (79 females; mean age 34.02 $\pm$ 13.8 years). Data on changes in upper limb motor function, assessed by the RULM, were extracted along with standard deviations and follow-up duration (12–28 months) from seven studies which reported pre- and post-treatment RULM scores. A random-effects meta-analysis estimated the pooled effect size with 95% confidence intervals (CI). An exploratory meta-regression evaluated the associa-

tion between RULM change and the proportion of SMA type 3 patients. Mean changes in RULM ranged from -0.71 to 2.76 points. The pooled effect size was 1.37 (95% CI 0.72–2.23; $p = .003$), indicating a statistically significant improvement. Considerable inter-study variability was observed, likely related to differences in baseline disability, age, and follow-up duration. Meta-regression showed no significant association between RULM improvement and the proportion of SMA type 3 patients ($\beta = 0.41$, $p = .87$)

Real-world evidence supports the effectiveness of risdiplam in improving upper limb motor function in adults with 5q-associated SMA, although results should be interpreted cautiously due to the limited number of studies.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P227 - Cod. 143497

EXECUTIVE FUNCTION DEVELOPMENT IN SPINAL MUSCULAR ATROPHY: A LONGITUDINAL CASE REPORT OF THREE CHILDREN IN THE DISEASE-MODIFYING THERAPY ERA

D’armini C.^{*}, Saraceni V., Branca A., Della Rocca R., Mandis N., Nobili S., Briganti M., Sancricca C., Frongia A.L.
C. D’Armini, Roma, Italy

The introduction of disease-modifying therapies (DMTs) has altered the natural history of Spinal Muscular Atrophy (SMA), leading to improved survival and motor outcomes (1). As children with SMA now achieve motor milestones that were previously unattainable, new areas of vulnerability have emerged, including cognitive and executive functioning (2). The aim of this study was to describe the longitudinal trajectory of executive functions in relation to neuropsychomotor development in three young children with SMA.

Two SMA 1 children and one presymptomatic child were assessed every six months over an 18-month period. Executive functions were evaluated using the FE-PS, a play-based assessment for children aged 2–6 years measuring inhibitory control, delay of gratification, and complex/interdependent abilities. Neuropsychomotor development was assessed with the Griffiths Scales, including cognitive, language, eye–hand coordination, personal–social–emotional, gross motor domains, and a Total Developmental Quotient.

Although motor scores improved in all patients over time, all children performed worse on tasks requiring motor involvement. Patient 1 demonstrated stable or improving cognitive abilities despite persistent motor and social–emotional difficulties. Patient 2 showed mild progressive executive improvements. Patient 3 displayed normal and improving cognitive and executive profiles alongside gradual motor gains.

Although limited by sample size and lack of standardized tests adapted to SMA patients, this study highlights individualized but overall improving executive and cognitive trajectories in children with SMA, paralleling motor development. Larger longitudinal studies are needed to better characterize executive outcomes and their relationship with motor progress.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P229 - Cod. 143459

EXPLORING HIGHER DOSES OF NUSINERSEN IN SPINAL MUSCULAR ATROPHY (SMA): INTEGRATED RESULTS FROM THE DEVOTE PART B AND ONWARD STUDIES

Mercuri E.M.^{*1}, Garcia Romero M.D.M.², Crawford T.³, Finkel R.⁴, Day J.W.⁵, Montes J.⁶, Sumner C.³, Paradis A.D.⁷, Sun P.⁷, Foster R.⁸, Gambino G.⁸, Littauer R.⁷, Fradette S.⁷, Farewell R.⁷

¹ Catholic University, Rome, Italy, ² Hospital La Paz, Madrid, Spain, ³ Johns Hopkins Hospital, Baltimore, MD, United States of America, ⁴ St. Jude Children's Research Hospital, Memphis, TN, United States of America, ⁵ Stanford University School of Medicine, Stanford, CA, United States of America, ⁶ Columbia University Irving Medical Center, New York, NY, United States of America, ⁷ Biogen, Cambridge, MA, United States of America, ⁸ Biogen, Maidenhead, United Kingdom

DEVOTE (NCT04089566; 3-part, Phase 2/3 trial) and ONWARD (NCT04729907; Phase 3 open-label long-term extension) evaluate an investigational higher-dose nusinersen regimen (two 50 mg loading doses 14 days apart, followed by 28 mg maintenance doses every 4 months) in participants with SMA.

DEVOTE Part B randomized (2:1) 75 treatment-naïve participants with infantile-onset SMA to 50/28 mg or 12/12 mg nusinersen. A prespecified matched sham group from ENDEAR (NCT02193074) (n = 20) served as the primary comparator for 50/28 mg (n = 50). Participants receiving 50/28 mg (baseline mean Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND] score: 20.9) showed statistically significant improvement over matched sham (baseline mean CHOP-INTEND: 23.6) on change in CHOP-INTEND from baseline to Day 183 (primary endpoint) (least-squares mean [LSM], +15.1 versus -11.1; LSM difference [95% confidence interval (CI)] 26.19 [20.7–31.7]; joint-rank test LSM, 42.9 versus 16.9; difference [95% CI]: 26.06 [17.9–34.2], p < 0.0001). Nusinersen 50/28 mg was generally well tolerated, with adverse events broadly consistent with 12/12 mg.

As of the interim data cut, ONWARD has enrolled 35 infantile-onset and 23 later-onset participants from Part B. The primary endpoint of ONWARD is safety, and longer-term 50/28 mg was generally well tolerated. Pre-dose evaluations of ONWARD Day 1 for CHOP-INTEND and HINE-2 in the infantile-onset cohort, and for Hammersmith Functional Motor Scale – Expanded and Revised Upper Limb Module in the later-onset cohort, showed consistent trends compared with DEVOTE. Collectively, these data show the longer-term efficacy and safety of 50/28 mg nusinersen.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P231 - Cod. 142705

EXPLORING THE TRAJECTORY OF SWALLOWING WITHIN PSYCHOMOTOR DEVELOPMENT IN SPINAL MUSCULAR ATROPHY TYPE 1: MOVING TOWARD

INTEGRATED CARE

Gandolfi S.^{*1}, Dosi C.¹, Parravicini S.¹, Arnoldi M.T.¹, Zanin R.¹, Biagi S.¹, Rinaldi L.², Masson R.¹

¹ Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy, ² University of Verona, Department of Innovation Medicine and Engineering, Verona, Italy

Spinal Muscular Atrophy type 1 (SMA type 1) is a genetic neuromuscular disease that typically presents before 6 months of age and is characterized by profound hypotonia, progressive muscle weakness, and early involvement of respiratory and bulbar musculature. Swallowing impairment (dysphagia) is a hallmark of SMA type 1 and significantly contributes to morbidity. Despite the documented benefits of disease-modifying therapies (DMTs) in terms of enhanced survival and motor outcomes, their impact on swallowing remains understudied.

This study aims to longitudinally characterize swallowing function in children with SMA type 1 treated with DMTs, while contextualizing these findings in relation to the patients' current motor abilities and cognitive performance.

A single-center, longitudinal, observational study was conducted at Besta, Milan (2021-2025). Swallowing function was evaluated with four validated scales (MAS, OrSAT, FILS, and p-FOIS), while motor and cognitive functions with CHOP-INTEND and age-appropriate cognitive tests. Patients were stratified by baseline swallowing status, therapy, and age at DMT initiation. Non-parametric analyses were used. Swallowing function showed no significant change over one year in the overall cohort or subgroups, despite significant motor improvement. Most swallowing scales, except swallowing safety, were moderately associated with motor and cognitive measures.

Swallowing function in children with SMA type 1 remained largely stable, while motor function significantly improved over one year, regardless of baseline swallowing status, DMT type and age at administration. These findings underscore the need for standardized, longitudinal assessments of swallowing, motor, and cognitive functions in the management of SMA type 1.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P233 - Cod. 143403

IMPACT OF DISEASE-MODIFYING TREATMENT ON RESPIRATORY OUTCOMES AFTER SCOLIOSIS SURGERY IN SMA PATIENTS: UPDATED ITASMAC REAL-WORLD DATA

Morando S.^{*1}, Brolatti N.¹, Coratti G.², Pedemonte M.³, Panicucci C.¹, Latinakis G.¹, De Sanctis R.⁴, Albamonte E.⁵, Catteruccia M.⁶, Zanin R.⁷, Bitetti I.⁸, Ticci C.⁹, Sacchini M.⁹, Berardinelli A.¹⁰, Filosto M.¹¹, Ricci F.¹², Sframeli M.¹³, Messina S.¹³, Varone A.⁸, Masson R.⁷, Trabacca A.¹⁴, Coccia M.¹⁵, Bruno I.¹⁶, Pera M.C.¹⁷, Pegoraro E.¹⁸, Agosto C.¹⁹, Pini A.²⁰, D'Amico A.⁶, Mongini T.¹², Sansone V.⁵, Pane M.², Mercuri E.², Canavese F.²¹, Bruno C.²², Trucco F.²³

¹ Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy, ² Pediatric Neurology, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Rome, Italy. Centro Clinico

NeMO, Fondazione Agostino Gemelli IRCCS, Rome, Italy, Rome, Italy, ³ Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Genoa, Italy, ⁴ Centro Clinico NeMO, Fondazione Agostino Gemelli IRCCS, Rome, Italy, Rome, Italy, ⁵ The NEMO Center in Milan, Neurorehabilitation Unit, University of Milan, ASST Niguarda Hospital, Italy, Milan, Italy, ⁶ Department of Neurosciences, Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, Rome, Rome, Italy, ⁷ Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, Milan, Italy, ⁸ Pediatric Neurology, Santobono-Pausilipon Children's Hospital, Neurology Unit, Naples, Italy, Naples, Italy, ⁹ Metabolic and Neuromuscular Unit Meyer Children's Hospital IRCCS, Florence, Italy, Florence, Italy, ¹⁰ Department of Child Neuropsychiatry (A.B.), Fondazione Istituto Neurologico Nazionale C Mondino Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Pavia, Italy, ¹¹ Department of Clinical and Experimental Sciences, University of Brescia (Italy), NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, Brescia, Italy, ¹² SC Neuropsichiatria Infantile, AOU Regina Margherita-Sant'Anna, Università di Torino, Torino, Italy, Torino, Italy, ¹³ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, Messina, Italy, ¹⁴ Scientific Institute IRCCS "E. Medea" (A.T.), Unit for Severe disabilities in developmental Age and Young Adults (Developmental Neurology and Neurorehabilitation), Brindisi, Brindisi, Italy, ¹⁵ Centro Clinico NeMO Ancona, AOU delle Marche, Ancona, Italy, Ancona, Italy, ¹⁶ Institute for Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy, Trieste, Italy, ¹⁷ Child Neuropsychiatry Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy, Pediatric Neurology, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Rome, Italy, Parma, Italy, ¹⁸ Neurology Unit, Azienda Ospedale Padova, Padua, Italy, Padua, Italy, ¹⁹ Department of Women's and Children's Health, University of Padua, Padua, Italy, Padua, Italy, ²⁰ Pediatric Neuromuscular Unit, Pediatric Neuropsychiatry Complex Unit, IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy, Bologna, Italy, ²¹ Department of Orthopedic and Traumatology, IRCCS Istituto Giannina Gaslini, Genoa, Italy, DISC-Dipartimento di Scienze Chirurgiche e Diagnostiche Integrate, University of Genova, Genova, Italy, Genoa, Italy, ²² Center of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy, ²³ Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy

Aim of this study was to confirm whether disease-modifying treatments (DMT) influenced post-arthrodesis respiratory trajectories in a broad, multicentre national cohort of patients with Spinal Muscular Atrophy (SMA).

Retrospective multicentre analysis of SMA patients included in the ITASMAC (Italian Spinal Muscular Atrophy Consortium) dataset who underwent scoliosis surgery between 2005 and 2025.

Cobb angle and respiratory function, including forced vital capacity (FVC), FVC% predicted, and peak cough flow (PCF), were analyzed before and after arthrodesis. Data were presented as median (IQR). Linear regression evaluated whether the Cobb improvement% was associated with FVC%pred improvement post-arthrodesis ($\Delta\text{FVC\%pred}$ [%]), and whether such changes differed between DMT-treated and DMT-naïve patients.

Fifty-seven non-ambulant patients were included (SMA types: I, n = 2; II, n = 45; III, n = 10) and were stratified into 29 DMT-treated and 28 DMT-naïve. Median age at scoliosis surgery, in both group, was 12 years (10.85–13.75), with a median DMT start age of 8.5

years (7.0–11.25).

Using percentage changes, DMT-treated showed a more favorable respiratory trend after arthrodesis ($\Delta\text{FVC\%}$ median +0.06 [−0.20; +0.29]) compared with naïve (−0.12 [−0.19; +0.02]).

Moreover, in DMT-treated patients, each 10% scoliosis correction (Cobb angle reduction) was associated with an average 7.8% increase in FVC% predicted ($p = 0.01$). This relationship was weaker/absent in DMT-naïve. Slopes differed significantly between groups (interaction $p = 0.007$), supporting a potential modulatory role of DMT on post-surgical respiratory response.

These results in a broad SMA cohort confirm a more favorable post-arthrodesis respiratory outcome in patients DMT-treated than in DMT-naïve patients suggesting a synergistic effect.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P235 - Cod. 143468

NEUROMUSCULAR SCLIOSIS IN SMA CHILDREN: CLINICAL FOLLOW-UP IN THE DMT ERA

Branca A.*, Saraceni V., Mandis N., D'Armini C., Della Rocca R., Onofri M., Briganti M., Sancricca C., Frongia A.L.
Fondazione UILDM Lazio ETS, Roma, Italy

Introduction: Neuromuscular scoliosis remains a significant challenge in Spinal Muscular Atrophy (SMA), even with disease-modifying therapies (DMTs). The acquisition of new motor milestones, combined with persistent axial weakness, leads to earlier onset and faster progression of scoliosis.

Methods: Six pharmacologically treated SMA individuals (aged 5 months–3 years) were monitored over three years with biannual assessments. Upper and lower segmental axial trunk rotation (SATR-U/L), total angle of trunk rotation (ATR), and pelvic obliquity (PO) were measured with a scoliometer. Cervical rotation (CR) and hip extension (HE) were measured with a Rippstein plurimeter. Thoracic and abdominal circumferences, their ratio, and chest expansion asymmetries were recorded.

Aim: to identify early predictive asymmetries in conditions where radiographic evaluation is unreliable, to support timely and personalized rehabilitative strategies.

Results: At baseline, two subjects had relevant scoliotic curves: Pt1 showed progressive PO and ATR increases over time, while Pt2 remained stable. Pt3 and Pt4 developed SATR and PO > 3° at 30 months; Pt5 and Pt6 showed no significant progression. Chest expansion asymmetry occurred in four subjects, all had a positive abdominal/thoracic ratio.

Discussion: Deformity onset often coincided with the achievement of independent sitting. Early intervention targeting asymmetries detected in HE and CR range of motion appears to be beneficial. Limitations include small sample size.

Conclusion: This protocol supports early, personalized rehabilitation and may serve as a useful adjunct in multidisciplinary care of SMA, despite the challenges in managing neuromuscular scoliosis.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P237 - Cod. 143244

PERCEIVED WELL-BEING DESPITE SEVERE MOTOR IMPAIRMENT: PATIENT-REPORTED OUTCOMES IN CHILDREN AND ADOLESCENTS WITH SPINAL MUSCULAR ATROPHY

Benedetti F.¹, De Pazzi C.², Soravia G.¹, Toffanello S.¹, Sartori S.³, Agosto C.³

¹ Dipartimento di Salute della Donna e del Bambino, Azienda Ospedale Università Padova, Padova, Italy, ² Scuola di Specializzazione in Pediatria, Università degli Studi di Padova, Padova, Italy, ³ Neurologia e Neurofisiologia Pediatrica, Dipartimento di Salute della Donna e del Bambino, Azienda Ospedale Università Padova, Padova, Italy

In pediatric patients with spinal muscular atrophy (SMA), motor function scales often indicate severe disability. However, how patients perceive their own functional status, remains poorly understood. Patient-reported outcomes (PROs) may provide complementary information to objective assessments.

This study aimed to explore patients' perception of their condition across multiple domains. A questionnaire investigating fatigability, breathing and voice, sleep and rest, and perceived vulnerability was

derived from a previously published instrument. Inclusion criteria were a clinical and/or genetic diagnosis of SMA and age ≥ 8 years.

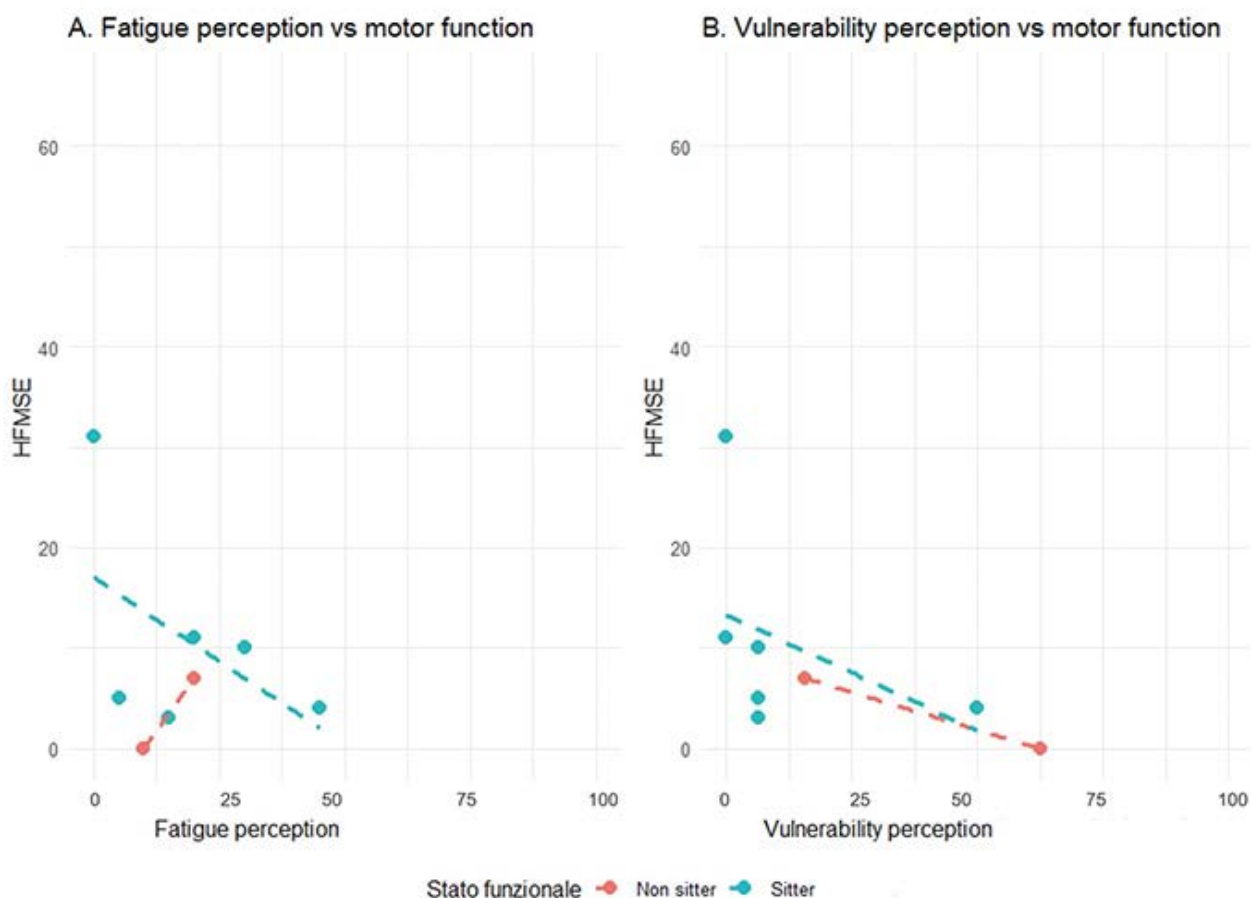
Eight patients were included (5 males), median age 18 years (12-19), 5 with SMA2 and 3 with SMA3. Most were sitters (2, 25%), and 3 were non-sitters (38%). All patients were receiving disease-modifying therapies. Motor function scores indicated severe impairment (median HFMSE 6; range 0-31; median RULM 19, range 0-36). The majority of participants reported low daytime fatigue, with breathing, sleep, or rest problems having little effect on everyday life. Feelings of vulnerability and dependence were generally less severe than expected based on objective assessments (Figure 1).

Despite severe motor impairment, adolescents with SMA reported relatively low fatigue and vulnerability perception. Preserved upper limb function may contribute to autonomy in daily activities and positively influence subjective well-being, supporting the integration of patient-reported outcomes into routine care and research.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P239 - Cod. 143464

PHASE 1 INTERIM RESULTS EVALUATING THE SAFETY, TOLERABILITY,



PHARMACOKINETICS, AND EXPLORATORY EFFICACY OF SALANERSEN FOR SPINAL MUSCULAR ATROPHY

Sansone V.^{*1}, Kotulska--Jóźwiak K.², Crawford T.³, Ziegler A.⁴, Fradette S.⁵, Sun P.⁵, Alexanian S.⁵, Inra J.⁵, Rubel C.⁵, Czerkowiec J.⁵, Heo J.⁵, Verone--Boyle A.⁵, Wu S.⁵, Liu Y.⁵, Foster R.⁶, Burton L.⁵

¹NeMO Clinical Center, Milan, Italy, ²Children's Memorial Health Institute, Warsaw, Poland, ³Johns Hopkins Hospital, Baltimore, MD, United States of America, ⁴Heidelberg University Hospital, Heidelberg, Germany, ⁵Biogen, Cambridge, MA, United States of America, ⁶Biogen, Maidenhead, United Kingdom

Salanersen (BIB115) is an investigational, intrathecally administered antisense oligonucleotide with novel modification to the backbone and similar mechanism of action, but higher potency, than nusinersen in nonclinical studies, enabling the potential to maximize clinical outcomes with dosing only once yearly.

This Phase 1 study (NCT05575011/EU CT 2023-505643-39) is evaluating the safety/tolerability, pharmacokinetics, and exploratory efficacy of salanersen. Part B evaluates open-label salanersen (40 mg or 80 mg doses) in pediatric participants (aged 0.5–12 years) with spinal muscular atrophy (SMA) previously treated with onasemnogene abeparvovec with suboptimal clinical status. Study objectives are to evaluate the safety/tolerability (primary) and pharmacokinetics (secondary) of salanersen.

An interim analysis was performed once the older participants in the 40 mg dose cohort (n = 8) had completed at least 1 year of follow-up. Salanersen was generally well tolerated at the 40 mg and 80 mg dose levels. In participants with elevated baseline plasma neurofilament levels, salanersen treatment was associated with a 70% reduction by Day 180, which was sustained over time. Of the 8 participants with 1-year follow-up available, 4 (50%) achieved new WHO motor milestones beyond what would be expected based on baseline functional status and time on previous treatment, and clinically meaningful improvements were observed on Hammersmith Functional Motor Scale – Expanded (mean +3.3-point improvement) and Revised Upper Limb Module (mean +5.3-point improvement).

The interim results of this study will inform the design of planned registrational trials in SMA. Updated interim analyses from the November 2025 data cut will be presented.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P241 - Cod. 143362

REHABILITATION NEEDS AND CARE MODELS IN SPINAL MUSCULAR ATROPHY: A REAL-WORLD ANALYSIS FROM AN ITALIAN COMMUNITY REHABILITATION CENTER

Briganti M.^{*1}, Branca A.², Saraceni V.², Rossi S.³, Torchia E.³, Orlando P.², Mandis N.², Della Rocca R.², D'Armini C.², Onofri M.², Robertazzi O.², Sancricca C.¹, Frongia A.L.⁴

¹(1) Fondazione UILDM Lazio, (2) Neurophysiopathology unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Rome, Italy, ²(1) Fondazione UILDM Lazio, Rome, Italy, ³(1) Fondazione UILDM Lazio, Rome

(3) Department of Neurosciences, Università Cattolica del Sacro Cuore, Rome, Italy, Rome, Italy, ⁴(4) Centro Clinico Nemo, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Rome, Italy

Spinal muscular atrophy (SMA) remains a chronic condition despite major diagnostic and therapeutic advances. Improved survival has shifted clinical priorities toward long-term functional limitations, particularly bulbar dysfunction and orthopedic complications. Recent evidences demonstrate that optimal outcomes cannot be achieved through drug therapy alone (1-2), emphasizing the importance of integrated, multidisciplinary, standards of care, including rehabilitation (3-8).

This observational study describes rehabilitative management of individuals with genetically confirmed SMA followed at Fondazione UILDM Lazio during 2024–2025.

Demographic, clinical, functional, and rehabilitative data were retrospectively collected from routine medical and rehabilitation records. The cohort showed marked heterogeneity in age, phenotype, motor abilities, and access to treatment. Sitters represented the largest functional group. Treated patients were significantly younger than untreated ones. Intensity progressively decreased from SMA type 1 to type 3.

Neuropsychomotor therapy predominated in pediatric care, while physiotherapy was central in older patients and in SMA type 2 and type 3.

In SMA type 1, the absence of non-sitters deviated from the expected natural history, reflecting early diagnosis and therapeutic intervention. Rehabilitation care started earlier and was more intensive and multidisciplinary in severe phenotypes, with SMA type 1 characterized by high weekly intensity and frequent respiratory and speech therapy. Mean weekly rehabilitation intensity progressively decreased from SMA type 1 to SMA type 3. This gradient is consistent with the increasing clinical complexity and need for early, comprehensive intervention in more severe phenotypes.

Rehabilitation in SMA represents a continuous, personalized pathway modulated by age and disease severity.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P243 - Cod. 143118

RISDIPLAM IN ADULT PATIENTS WITH 5Q SPINAL MUSCULAR ATROPHY: A SINGLE-CENTER EXPERIENCE

Vacchiano V.^{*1}, Baroncelli A.², Briganti E.³, Donadio V.⁴, Giannoccaro M.P.⁴, Rizzo G.⁵, Not R.⁶, Rocco L.⁷

¹UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna; Centro Clinico NeMO, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ²Medicina e Chirurgia, Università di Bologna, Bologna, Italy, ³Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna; UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ⁴UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna; Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ⁵UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche

di Bologna, Bologna, Italy, ⁶ UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna; UO DATeR Riabilitazione Territoriale, AUSL Bologna, Bologna, Italy, ⁷ UOC Clinica Neurologica, IRCCS Istituto delle Scienze Neurologiche di Bologna; Centro Clinico NeMO, IRCCS Istituto delle Scienze Neurologiche di Bologna; Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy

Risdiplam is the first approved oral therapy for spinal muscular atrophy (SMA). Evidence of its effectiveness in adults has so far relied mainly on small cohorts with short-term observational data.

The present study evaluates the long-term efficacy and safety of risdiplam in adult patients.

We prospectively enrolled adult SMA patients treated with risdiplam from January 2022 to December 2025. Hammersmith Functional Motor Scale–Expanded (HFMSE), Revised Upper Limb Module (RULM), forced vital capacity (FVC) and serum creatinine levels were assessed at baseline and every six months.

Overall, 19 patients (8 males, median age 37 years, range 20–78) were enrolled, with a median follow-up of 33.1 months. One patient discontinued treatment due to tremors and tachycardia, and another died of pneumonia after five months of treatment. No other serious adverse events were reported.

HFMSE strongly correlated with RULM ($p = 0.924$, $p < 0.001$) and FVC ($p = 0.905$, $p < 0.001$), while RULM also correlated with FVC ($p = 0.821$, $p = 0.001$). Creatinine levels moderately correlated with HFMSE ($p = 0.673$, $p = 0.006$) and RULM ($p = 0.606$, $p = 0.017$). 76.4% of patients had stable HFMSE scores, 11.8% declined (mean difference, MD -2.5), and 11.8% slightly improved (MD $+1.5$). RULM was stable in 47% of patients, increased in 29.5% (clinically meaningful in 17.6%), and decreased in 23.5%. Among 12 patients assessed for FVC, 33.3% declined (all SMA2) and 66.7% improved (four SMA2, four SMA3). Creatinine levels did not change significantly over time (MD -0.086 , $p = 0.53$).

Overall, functional motor scales remained stable, with some patients showing meaningful improvements. Most patients experienced improved respiratory function.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P245 - Cod. 142780

SCOLIOSIS IN PATIENTS WITH SPINAL MUSCULAR ATROPHY TREATED WITH DISEASE-MODIFYING THERAPIES: A PILOT OBSERVATIONAL STUDY

Ait Allali N.^{*1}, Risi B.², Damioli S.¹, Giovanelli G.¹, Franchi E.¹, Gilberti G.³, Sorgente A.¹, Garletti G.¹, Nicolis F.¹, Puzzi M.¹, Garofali F.¹, Carugati R.¹, Pianto S.¹, Urbano I.¹, Colombi C.¹, Ottelli E.¹, Ferrari E.¹, Padovani A.⁴, Filosto M.⁵

¹NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, Brescia, Italy, ²NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy; Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, Brescia, Italy, ³NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, Italy, ⁴Department of Clinical and Experimental Sciences, University of Brescia,

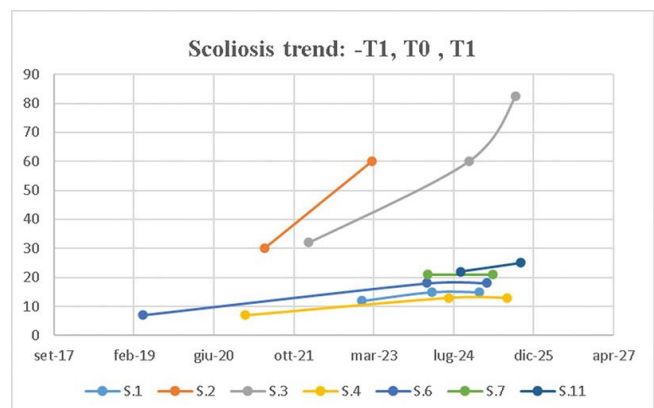
Brescia, Italy; Unit of Neurology, ERN EURO-NMD Center ASST Spedali Civili, Brescia, Italy, Brescia, Italy, ⁵NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy ; Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy ~

Disease-modifying therapies (DMTs) have modified the clinical course of spinal muscular atrophy (SMA), improving survival and motor outcomes. Nonetheless, scoliosis remains frequently observed.

Nine SMA patients receiving DMTs (3 SMA1, 6 SMA3; mean age 17.6 ± 13.1 years) were enrolled at baseline (T0). Scoliosis was assessed using Cobb angle. Clinical history and evaluations were collected including CHOP-INTEND, HFMSE, RULM, MFM-32, forced vital capacity (FVC), SMA Independence Scale–Clinical Report (SMAIS-CR) and SF-36 questionnaire. Associations between Cobb angle and clinical measures were explored using Spearman's rank correlation at baseline and after 1 year follow-up (T1).

At baseline, scoliosis was observed in 78% of patients ($n = 7$). SMA 1 patients presented more severe scoliosis (mean Cobb angle at T0: $45.0^\circ \pm 26.0^\circ$, at T1: $48.8^\circ \pm 47.7^\circ$), with one patient undergoing stabilization intervention. SMA 3 patients showed milder curves (mean Cobb angle at T0: $18.5^\circ \pm 4.0^\circ$, at T1: $19.3^\circ \pm 5.1^\circ$). Associations with Cobb angle were found at T0 with RULM ($r = -0.832$, $p = 0.040$), at T1 with FVC in liters ($r = 0.900$, $p = 0.037$) and SMAIS-CR ($r = -0.900$, $p = 0.037$). These associations should be interpreted cautiously, as increases in absolute FVC may reflect growth or treatment-related effects rather than respiratory function changes per se.

In this small exploratory-cohort, scoliosis was frequent in SMA patients receiving DMTs and appeared to co-occur with motor performance and daily functioning. Larger longitudinal studies are needed to better define scoliosis trajectories and clinical relevance in the DMTs-era.



SPINAL MUSCULAR ATROPHY (SMA)

Abstract P247 - Cod. 142789

SINGLE-CENTER LONG-TERM FOLLOW-UP OF 18 PATIENTS WITH SPINAL MUSCULAR ATROPHY (SMA) TREATED WITH RISDIPLAM

Bestetti R.M.^{*1}, Bestetti R.M.³, Bertella E.¹, Giovanelli G.¹, Caria

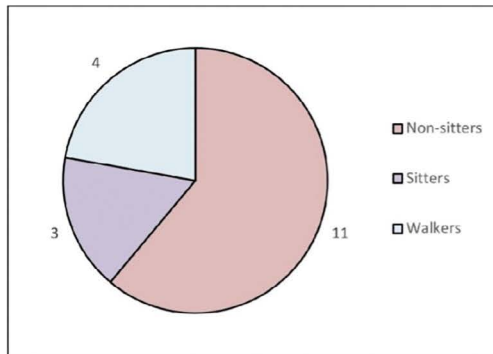


Fig.1: Patients divided by SMA function

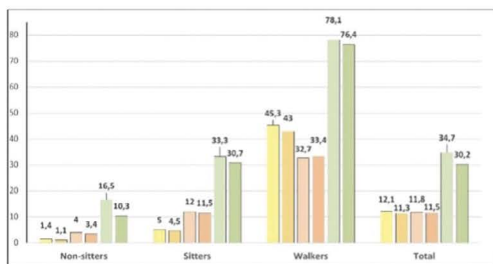


Fig.2: Mean basal and follow-up HFMSE (yellow shades), RULM (orange shades) and MFM-32 (green shades) scores in all patients divided by SMA function.

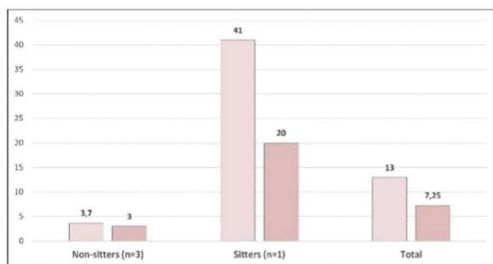


Fig.3: Mean basal and follow-up CHOP-INTEND scores in SMA1 patients.

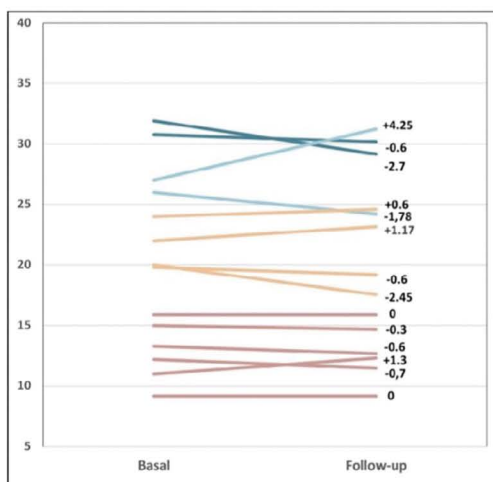


Fig.4: BMI scores at baseline and follow-up (n=14) [underweight: purple; normal weight: orange; overweight: light blue; obese: blue].

F.¹, Ait Allali N.¹, Garofali F.¹, Carugati R.¹, Gilberti G.¹, Poli L.², Bozzoni V.², Galli J.³, Galli J.⁴, Padovani A.², Padovani A.³, Filosto M.¹, Filosto M.³, Risi B.¹, Risi B.⁵

¹ NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, Brescia, Italy, ² Unit of Neurology, ASST Spedali Civili, Brescia, Italy, ³ Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁴ Unit of Child and Adolescent Neuropsychiatry, ASST Spedali Civili, Brescia, Italy, ⁵ Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy

The mean treatment follow-up was 35,4 months. Our sample included 4 patients with SMA1, 5 with SMA2, and 9 with SMA3. Changes in life endpoints (respiratory/nutritional support) and motor outcomes were assessed.

We aim to describe the clinical findings and evolution of a cohort of SMA patients treated with Risdiplam.

At baseline, 61.1% were non-sitters, 16.7% were sitters, and 22.2% were walkers. Swallowing impairment was present in 55.6% of patients, with five patients receiving feeding via PEG (n = 4 SMA1, n = 1 SMA2). Non-invasive ventilation (NIV) was used by 27,7% of patients; 72.2% used a cough-assist device. All SMA1 patients had a tracheostomy. No changes in these parameters were observed. The mean HFMSE score in SMA2-3 patients decreased from 12,1/66 to 11,3/66 points. The mean RULM score in SMA2-3 patients, changed from 11.8/37 to 11.5/37. The mean MFM-32 score (n = 12) declined from 34.7% to 30.2%. The mean CHOP-INTEND score in SMA1 patients (n = 4) decreased from 13/64 to 7,25/64.

Regarding BMI all underweight patients remained in the same category, whereas those initially classified as obese (n = 1), overweight (n = 1), and normal weight (n = 1) shifted to the immediately lower categories. Regarding adverse events, one patient reported asthenia and one discontinued treatment due to subjective lack of efficacy.

We observed substantial clinical stabilization of bulbar and respiratory function in all patients. A mild worsening was detected across all motor scales, with only a slight improvement in RULM scores among walkers. BMI remained stable in underweight patients, while normal-weight and overweight/obese showed a general trend toward weight reduction.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P249 - Cod. 143322

SLEEP PHENOTYPES AND RESPIRATORY DISTURBANCES IN SPINAL MUSCULAR ATROPHY: A SYSTEMATIC REVIEW OF CLINICAL EVIDENCE

Gnazzo M.^{*1}, Baldini V.¹, Varallo G.², Pisanò G.², Biscarini F.¹,

Carotenuto M.³, Pizza F.¹, Fiorillo A.⁴, Pera M.C.⁵, Plazzi G.²

¹ Department of Biomedical and Neuromotor Sciences, Bologna, Italy, ² 1.

Department of Biomedical, Metabolic and Neural Sciences, Modena, Italy,

³ 3. Clinic of Child and Adolescent Neuropsychiatry, Department of Mental

Health, Physical and Preventive Medicine, University of Campania "Luigi

Vanvitelli", Napoli, Italy, ⁴ Department of Psychiatry, Napoli, Italy, ⁵ Child

neuropsychiatry Unit, Department of Medicine and Surgery, University of

Parma, Parma, Italy

Spinal muscular atrophy (SMA) is a rare neuromuscular disorder in

which sleep-related respiratory disturbances are common and may worsen morbidity and quality of life. However, systematic evidence on sleep architecture, sleep-disordered breathing (SDB), and treatment outcomes in SMA is limited.

To provide a comprehensive synthesis of the existing evidence on sleep characteristics, respiratory disturbances, and the impact of non-invasive ventilation (NIV) in SMA patient treated with disease-modifying therapies (DMTs) across lifespan.

Twenty-seven studies (ranging from single case reports to cohorts of > 100 patients) revealed that SDB, particularly obstructive and central apneas, is highly prevalent in SMA types 1–3. Sleep architecture abnormalities include reduced REM sleep, increased N1, and abnormal cyclic alternating pattern (CAP) indices, suggesting impaired arousability. Nocturnal hypoventilation may occur even without overt hypoxemia. Interventions with NIV consistently reduced AHI and improved nocturnal oxygenation. DMTs showed potential benefits in stabilizing or improving sleep outcomes, though residual SDB remains common.

Sleep disturbances in SMA are multifactorial, reflecting both respiratory muscle weakness and central nervous system involvement. NIV remains essential in managing SDB, while DMTs hold promise for improving long-term outcomes. Regular polysomnography and respiratory assessments are recommended in the follow-up of all type of SMA patients.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P251 - Cod. 143038

TITIN AND THE MUSCLE-BRAIN AXIS: A PROMISING BIOMARKER FOR NUSINERSEN THERAPY ACROSS SMA CSF TRANSCRIPTOME AND RADIOLOGICAL PERSPECTIVE

Dragoni F.¹, Dainesi M.I.¹, Asteggiano C.¹, Di Gerlando R.¹, Minucchi E.², Pichiecchio A.¹, Berardinelli A.L.¹, Gagliardi S.*¹

¹IRCCS Mondino, Pavia, Italy, ²University of Pavia, Pavia, Italy

Recent interest has focused on understanding SMA beyond motor neurons, particularly the role of cerebrospinal fluid (CSF) as a source for diagnostic and prognostic biomarkers.

This study investigates the CSF RNA transcriptome in adult SMA Type III patients to identify potential biomarkers by RNA-seq. Samples were collected at baseline (T0) and at multiple time points after Nusinersen treatment (T4, T6, T8, T10, T13, and T16). Differentially expressed (DE) RNAs were identified by comparing each post-treatment time point to the baseline. We correlated the transcriptomic data with muscular radiological observations (Fat Fraction, Cross-Sectional Area, Intramuscular Fat Fraction) and motor function parameters (Hammer-smith Functional Motor Score Expanded and 6-minute walk test). A progressive decrease in the number of DE transcripts was observed with a peak at T4 (115 transcripts) and T6 (229 transcripts), followed by a plateau. Pathway analysis of shared transcripts between T4 and T16 time points revealed a strong enrichment related to muscle structure and function, the muscle structural proteins Titin (TTN) and Nebulin (NEB) were the most prominent genes. Titin levels

were maximally upregulated at T4 and decreased with therapy with negative correlation with motor function scores.

This suggests that Titin levels may serve as effective marker for treatment efficacy. The CSF RNA signature in adult-onset SMA patients, particularly Titin, shows a correlation with clinical improvements following Nusinersen therapy. This study identifies Titin and Nebulin as promising biomarkers for monitoring treatment efficacy and suggests that future research should explore the role of Nusinersen in restoring muscle health in SMA.

SPINAL MUSCULAR ATROPHY (SMA)

Abstract P253 - Cod. 142693

WEARABLE SENSORS DETECT POSTURAL ABNORMALITIES IN SPINAL MUSCULAR ATROPHY

Risi B.*¹, Ait Allali N.², Franchi E.², Rizzardi A.³, Ferullo L.², Caria F.², Bestetti R.M.⁴, Poli L.⁵, Bozzoni V.⁵, Galli J.⁶, Padovani A.⁷, Pilotto A.⁸, Filosto M.⁹

¹NeMO-Brescia Clinical Center for Neuromuscular Diseases; Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, ²NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ³Laboratory of Digital Neurology and Biosensors, University of Brescia; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁴NeMO-Brescia Clinical Center for Neuromuscular Diseases; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁵Unit of Neurology, ERN EURO-NMD Center ASST Spedali Civili, Brescia, Italy, ⁶Unit of Child and Adolescent Neuropsychiatry, ASST Spedali Civili; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁷Unit of Neurology, ERN EURO-NMD Center ASST Spedali Civili; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁸Unit of Neurology, ERN EURO-NMD Center ASST Spedali Civili; Laboratory of Digital Neurology and Biosensors, University of Brescia; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ⁹NeMO-Brescia Clinical Center for Neuromuscular Diseases; Unit of Neurology, ERN EURO-NMD Center ASST Spedali Civili; Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

Preclinical studies suggest the presence of postural and coordination deficits in spinal muscular atrophy (SMA), possibly related to altered sensorimotor neurotransmission. However, postural function has been poorly investigated in SMA patients. This pilot study evaluated postural function in ambulant SMA patients using wearable sensors. Two pairs of SMA3 siblings (two sisters and two brothers; mean age 35.6 years) underwent a sensor-based assessment of balance, including anticipatory postural adjustments (APA), double support (%), foot elevation at midswing (cm), lateral step variability (cm) and circumduction (cm). In the sisters, postural control was further assessed using the Romberg test with eyes open (EO) and closed (EC), measuring sway area (°), jerk (m²/s⁵), and path length (m/s²). Results were compared with normative data and with two age-matched patients with late-onset Pompe disease (LOPD).

Compared with normative values, M1 exhibited reduced APA-related first-step range of motion and left foot circumduction; F1 showed reduced elevation of the left foot at midswing, reduced circumduction of both feet, and increased stance time of the right foot; F2 exhibited

only reduced left foot circumduction. M2 showed no gait abnormalities.

In the Romberg test, both sisters exhibited increased sway parameters, particularly under EC conditions. Motor function scores confirmed greater impairment in the younger siblings (M1 and F1). LOPD patients showed normal parameters with EO, with abnormalities observed in only one patient under EC.

These preliminary findings indicate the presence of postural deficits in ambulant SMA patients. Larger studies are needed to clarify the relationship between postural impairment and motor function.

FRIDAY, MAY 15TH, 2026

POSTER SESSION NEUROPATHIES | even numbers

15:00-16:30

Chairs: Edoardo Canale, Emanuele Cassano

CHILDHOOD NEUROPATHIES

Abstract P012 - Cod. 143512

EARLY PERIPHERAL NERVE INVOLVEMENT IN ZELLWEGER SPECTRUM DISORDER: ELECTROPHYSIOLOGICAL AND ULTRASOUND FINDINGS

Bruno G.^{*1}, Pascarella A.², Rubino A.³, Nigro S.¹, Di Sarno I.³, Ferrara D.⁴, Esposito F.⁴, Varone A.¹, De Martino B.³

¹ Department of Neurosciences, Paediatric Neurology Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy, ² Chronic and Multifactorial Diseases Unit, Department of Paediatrics, Santobono-Pausilipon Children's Hospital, Naples, Italy, ³ Department of Neurosciences, Paediatric Neurophysiopathology Unit, Santobono-Pausilipon Children's Hospital, Naples, Italy, ⁴ Radiology Department, Santobono-Pausilipon Children Hospital, Naples, Italy

Zellweger Spectrum Disorder (ZSD) is a peroxisomal biogenesis disorder characterized by multisystem involvement, including central and peripheral nervous system abnormalities. Peripheral neuropathy is frequently reported, yet its structural and functional characterization in early infancy remains limited. We describe the electrophysiological and nerve ultrasound findings in a genetically confirmed neonatal ZSD case

A neonate presenting with severe hypotonia, dysmorphic features, early-onset epilepsy, and neuroradiological abnormalities suggestive of a peroxisomal disorder underwent metabolic testing, next-generation sequencing (NGS), nerve conduction studies (NCS), and high-resolution nerve ultrasound

Brain MRI showed white matter volume reduction, delayed myelination of pyramidal tracts, pachygyria, polymicrogyria, and germinolytic cysts. Plasma very long-chain fatty acids were markedly elevated (C26:0 4.97 μ M/L; C26:0/C22:0 ratio 0.455). NGS identified

compound heterozygous pathogenic variants in PEX6 (c.1947del; c.2245G > A), confirming ZSD. Nerve conduction studies demonstrated a sensorimotor polyneuropathy consistent with predominant dysmyelination. High-resolution nerve ultrasound revealed diffuse, symmetric enlargement of peripheral nerves with increased cross-sectional area and altered fascicular echotexture, indicating structural remodeling.

This case highlights early and severe peripheral nerve involvement in ZSD. The combination of axonal dysfunction on electrophysiology and diffuse nerve enlargement on ultrasound suggests a complex neurodegenerative process possibly involving secondary dysmyelination. Multimodal assessment integrating nerve conduction studies and ultrasound may enhance phenotypic characterization and provide a non-invasive tool for monitoring peripheral nerve involvement in peroxisomal disorders.

CHILDHOOD NEUROPATHIES

Abstract P014 - Cod. 143483

INCIDENCE OF PERIPHERAL NERVOUS SYSTEM AND ASSESSMENT OF MOTOR PERFORMANCE USING IMUS IN PATIENTS WITH ONCOHEMATOLOGICAL DISORDERS UNDERGOING STEM CELL HEMATOPOIETIC TRANSPLANT (HSCT): PRELIMINARY NEUROPSYCHOLOGICAL RESULTS FROM A PROSPECTIVE STUDY

Di Pisa V.^{*1}, Dimatteo K.², Gottardi F.³, Carvelli A.², Capoferri E.¹, Casanova M.¹, Masetti R.², Cordelli D.M.², Fetta A.²

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neuropsichiatria dell'Età Pediatrica, Bologna, Italy, ² Department Of Medical And Surgical Sciences (dimec), University Of Bologna, Bologna, Italy, ³ Pediatric Hematology and Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy

Allogeneic hematopoietic stem cell transplantation (HSCT) is a life-saving treatment associated with a broad spectrum of neurological complications. Peripheral neuropathy (PN) is relatively frequent yet remains poorly characterized; moreover, current evidence is mainly derived from adult populations. Predictive and prognostic markers are lacking, leading to delayed diagnosis and an increased risk of long-term neurological sequelae.

To describe the incidence and characteristics of post-HSCT PN diagnosed by electroneurography (ENoG) in a paediatric population. Prospective observational cohort study including patients aged 0–18 years undergoing HSCT. Pediatric modified Total Neuropathy Score (Ped-mTNS) and EnoG results performed 30–60 days before HSCT (T0), 30–60 days (T1), and 6–12 months (T2) after HSCT were collected. The study was funded by the Fondazione del Monte Translational Research Grant 2023.

Fourteen patients were enrolled (4 females, 10 males; median age 12 years, IQR 5–15). Twelve had leukemia and two primary immunodeficiencies. Four patients had pre-existing axonal PN. Median Ped-mTNS increased from 0.5 at T0 to 4 at T1 ($\Delta = +3.5$). 3 patients had new-onset PN after HSCT (1 axonal, 2 demyelinating).

One patient developed critical illness myopathy. At last follow-up, PN persisted in three patients.

New onset PN occurred in ~30% of patients, with early onset and a predominantly demyelinating pattern, suggesting inflammatory mechanisms. Neurophysiological monitoring may support early identification in clinical practice. Completion of this study, including laboratory and kinematic biomarkers, will allow identification of reliable predictive markers. Larger patient cohorts are required to validate these findings.

CHILDHOOD NEUROPATHIES

Abstract P016 - Cod. 142968

MPV17-RELATED AXONAL NEUROPATHY WITH EARLY AND PROGRESSIVE COURSE: REPORT OF AN ITALIAN FAMILY

Danti F.R.^{*1}, Baratta S.², Balistreri F.², Cazzato D.³, Izzo M.G.A.³, Magri S.², Moroni I.¹

¹ Department of Pediatric Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Unit of Medical Genetics and Neurogenetics, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³ Neurophysiopathology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

MPV17 mutations are classically associated with mitochondrial DNA depletion syndrome type 6 (MTDPS6), characterized by early-onset liver failure and multisystem involvement often including neuropathy. More recently, MPV17 variants have been linked to pure axonal sensorimotor neuropathy (CMT2EE).

We report clinical, neurophysiological and genetic data from two siblings with early-onset CMT2 carrying MPV17 variants.

The patients are sisters aged 19 and 9 years, born to healthy, non-consanguineous parents, with normal early motor development. Patient 1 developed gait disturbances, frequent falls, and foot deformities at 4 years. By age 6, she showed distal weakness, steppage gait, and sensory deficits. Nerve conduction studies revealed severe axonal sensorimotor neuropathy. The disease progressed to loss of independent ambulation at 17 years, with severe distal weakness, near-complete bilateral foot paralysis, mild proximal involvement, and marked superficial and deep sensory loss extending to the thighs.

Patient 2 presented at 5.6 years with running difficulties, foot deformities, and early loss of vibratory sensation. Neurophysiological assessment at 8 years showed findings similar to her sister, consistent with a severe axonal sensorimotor neuropathy. Liver function, brain MRI, ophthalmological and audiological examinations, and cognitive assessment were normal in both patients. Whole-exome sequencing identified compound heterozygous MPV17 variants: c.122G > A (p.Arg41Gln) and c.234_242delTGGACCCAC (p.Gly79_Thr81del), inherited from healthy parents.

To date, MPV17-related pure CMT2 has been reported in only 5 families, usually with later onset and milder progression.

We report the first Italian family with early-onset, severe and progressive CMT2EE, expanding the phenotypic spectrum and supporting MPV17 testing in early-onset axonal CMT2.

CHILDHOOD NEUROPATHIES

Abstract P018 - Cod. 143388

NERVE ULTRASOUND AND ELECTROPHYSIOLOGY AS CORRELATES OF CMTES SEVERITY IN PEDIATRIC CHARCOT-MARIE-TOOTH 1A DISEASE

Di Sarno I.^{*2}, Rubino A.², Bruno G.³, Esposito F.⁴, Ferrara D.⁴, De Martino B.M.¹

¹ UOSD Neurofisiopatologia clinica, Napoli, Italy, ² UOSD Neurofisiopatologia clinica, AORN Santobono-Pausilipon, Napoli, Italy, ³ UOC Neurologia, AORN Santobono-Pausilipon.it, Napoli, Italy, ⁴ UOSD Diagnostica per Immagini, AORN Santobono-Pausilipon.it, Napoli, Italy

Charcot-Marie-Tooth 1A disease (CMT1A) is a complex inherited neuropathy whose evaluation relies on clinical scales and neurophysiology. While electroneurography remains the reference technique, nerve ultrasound is increasingly used to non-invasively quantify structural nerve changes. This study aimed to assess the clinical usefulness of nerve ultrasound in CMT1A by testing its association with neurographic measures and clinical severity (CMTES), and by evaluating whether ultrasound or neurographic parameters predict clinical impairment.

Thirteen patients were recruited at our Neurophysiology Center. Clinical severity was assessed using the CMTES, and nerve ultrasound and electroneurography were performed. Composite variables were calculated by summing measures from the ulnar, posterior tibial, and deep peroneal nerves for proximal compound muscular action potential (PCMAP), distal compound muscular action potential (DCMAP), and proximal cross-sectional area (PCSA), whereas distal cross-sectional area (DCSA) was derived from the ulnar and posterior tibial nerves only. Correlation analyses and linear regression models were performed.

CMTES severity showed a significant correlation with proximal ultrasound/electrophysiology metrics, specifically with composite PCSA ($r = 0.573$, $p = 0.041$) and composite PCMAP ($r = -0.747$, $p = 0.003$), whereas correlations with distal parameters were not significant. Only composite PCMAP independently predicted CMTES ($B = -1.221$, $p = 0.039$; 95% CI -2.365 to -0.077).

These findings support the central role of electrophysiology and suggest that ultrasound-derived proximal morphology tracks disease burden. Overall, these preliminary findings reinforce nerve ultrasound as a confident, promising adjunct to routine CMT assessment.

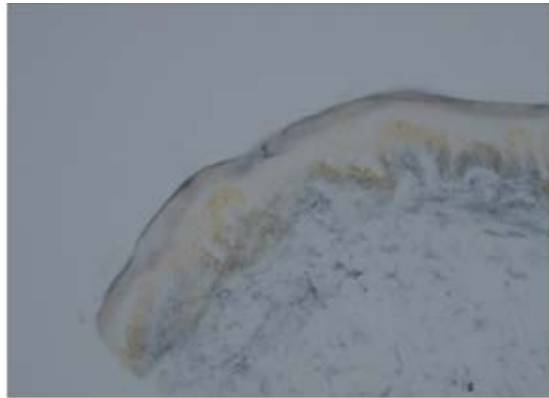
CHILDHOOD NEUROPATHIES

Abstract P020 - Cod. 143369

SMALL FIBER NEUROPATHY IN A PEDIATRIC PATIENT WITH KBG SYNDROME

Venturi C.B.³, D'Annunzio G.¹, Tantari G.¹, Massucco S.³, Leoncini G.², Trigiante M.^{*3}, Nozza P.³, Schenone A.³

¹ IRCCS Istituto G. Gaslini, Genova, Italy, ² Università degli studi di Genova, Genova, Italy, ³ Università degli studi di Genova, IRCCS AOM Ospedale Policlinico San Martino, Genova, Italy



A



B

(Fig.1) Skin biopsies of a patient's distal leg with normal intraepidermal nerve fiber density 20x (B). Skin biopsies of the patient's with KBG syndrome distal leg with significantly reduced intraepidermal nerve fiber density 20x (A).

KBG Syndrome (KBGS) is a rare genetic disorder caused by mutations in the ANKRD11 gene, typically presenting with macrodontia, craniofacial dysmorphism, short stature and developmental delays. While neurological issues like hypotonia and EEG abnormalities are common, this report highlights a potential new association with Small Fiber Neuropathy (SFN). SFN specifically affects small peripheral nerve fibers, leading to sensory disturbances and autonomic dysfunction.

To describe a possible new manifestation of SNF in KBGS.

The study focuses on a 4-year-old girl diagnosed with KBGS, displaying characteristic facial features, mild global developmental delay and emotional and attentional dysregulation. Her medical history was complicated by gestational diabetes, hypoglycemic episodes and fluctuating fasting glucose levels. Despite these metabolic concerns, extensive testing ruled out beta-cell autoimmunity, celiac disease and glycogenosis.

Between ages three and four, the patient developed worsening gait disturbances and lower limb clumsiness. Clinical examinations revealed hypotonia and absent deep tendon reflexes in the legs. While brain MRI, EEG and standard nerve conduction studies (which assess large fibers) were normal, a sudomotor evaluation indicated autonomic abnormalities in the lower limbs, prompting further investigation for SFN.

A skin biopsy was performed to quantify intraepidermal nerve fiber density (IENFD). Results showed significant denervation in the distal

leg and fragmented fiber morphology in the proximal thigh. As other causes of neuropathy were excluded (diabetes, autoimmunity, toxins, Fabry disease, inherited neuropathies), this case suggests that SFN may be an underdiagnosed manifestation of KBGS. Consequently, clinicians should consider SFN when KBG patients present with unexplained sensory or autonomic symptoms.

GENETIC NEUROPATHIES

Abstract P066 - Cod. 143357

ANOTHER MPZ VARIANT ASSOCIATED WITH LATE-ONSET CMT2

Saveri P.^{*1}, Crivellari L.¹, Dalla Bella E.², Magri S.³, Balistreri F.³, Marucci G.⁴, Izzo M.⁵, De Grado A.⁵, Lanteri P.⁵, Pisciotto C.¹, Pareyson D.¹

¹ Rare Neurological Diseases Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Neuroalgology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ³ Medical Genetics and Neurogenetics Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ⁴ Neuropathology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ⁵ Neurophysiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy

MPZ-related neuropathies show wide phenotypic heterogeneity, ranging from early-onset demyelinating CMT1B to later-onset predominantly axonal forms (CMT2).

We report an Italian family carrying a heterozygous MPZ variant, c.253G > A (p.Gly85Arg), associated with late-onset axonal neuropathy.

The proband, a 73-year-old male, developed progressive distal sensorimotor disturbances from age 63. Neurological examination revealed distal weakness and sensory loss in the lower limbs, absent deep tendon reflexes, and steppage-ataxic gait. Electrophysiological studies showed a moderate-to-severe axonal sensorimotor polyneuropathy, predominantly affecting the lower limbs, with associated carpal tunnel syndrome (CTS). Sural nerve biopsy demonstrated chronic axonal neuropathy with regeneration. Proband's findings are summarized in the Table. Family history was notable for late-onset neuropathy in the proband's mother. The same MPZ variant was found: in the proband's younger sister (57 years), whose only clinic-electrophysiological abnormalities were mild thenar atrophy and slight distal neurogenic changes with CTS; in the proband's daughter (40 years) who was asymptomatic with a normal neurological examination. The MPZ c.253G > A (p.Gly85Arg) variant, absent from population databases, is predicted to be probably damaging by multiple in silico tools. Molecular modelling indicated that it causes local structural alterations in a conserved functional domain of the MPZ protein, potentially affecting stability and interactions.

Notably, the same variant has been reported in a Hungarian CMT series¹, although without phenotypic description. Despite incomplete segregation, probably related to late onset and age-dependent penetrance, combined clinical, electrophysiological and structural data support classification of MPZ p.Gly85Arg as a likely pathogenic variant associated with late-onset CMT2.

¹ Milley GM et al., 2018.

Table. Clinical and electrophysiological findings of the proband

- Age at examination (years) / sex: 73 / M
- Age at onset (years) / symptoms: 63 / Foot hypoesthesia, imbalance, steppage gait
- Motor symptoms (legs): Steppage gait
- Proximal/distal weakness UL: – / –
- Proximal / distal weakness LL: ++ / ++ (foot dorsiflexion MRC: 2/5 R; 3/5 L)
- Ankle deep tendon reflexes: Reduced
- Joint position sense UL /LL: Normal /Impaired
- Vibration sense UL /LL: Reduced at knees
- Pinprick UL / LL: Reduced at feet
- Light touch UL / LL: Reduced at feet
- Pes cavus: Absent
- Additional clinical features: Postural tremor; CTS
- Comorbidities: DM2 since 71 (well controlled); large B-cell lymphoma at 71 (in full remission; no neurotoxic medication)
- CMTESv2: 10 / 28
- Sural nerve biopsy: Axonal sensorimotor polyneuropathy; chronic axonal neuropathy with regeneration

Motor NCS**Sensory NCS**

Nerve	DML (ms)	dCMAP (mV)	MNCV (m/s)	Nerve	SNCV (m/s)	SNAP (μV)
Median (L)	4.38	12.1	41.2	Median (L)	40	10.3
Median (R)	4.13	8.7	40.9	Ulnar (L)	51	24.8
Ulnar (L)	2.15	13.3	51.2	Sural (R)	37	1.6
Ulnar (R)	2.33	16.3	50.5			
Peroneal (L)	–	0.4	32.3			
Peroneal (R)	–	NR	–			
Tibial (L)	–	1.2	35.1			

Abbreviations: UL, upper limbs; LL, lower limbs; MRC, Medical Research Council scale; CTS, carpal tunnel syndrome; DM2, type 2 diabetes mellitus; CMTES, Charcot-Marie-Tooth Examination Score; NCS, nerve conduction studies; DML, distal motor latency; dCMAP, distal compound muscle action potential; MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential; NR, no response

GENETIC NEUROPATHIES**Abstract P068 - Cod. 143069****BALANCE CONFIDENCE AND REHABILITATION IN INDIVIDUALS WITH CANVAS**

Zuccarino R.^{*}, Stano S., Ferrari V.
Centro NeMO Trento, Trento, Italy

Balance and function impairment is common in individuals with CANVAS

The aim of this study was to evaluate the balance confidence, fall frequency, and perceived effect of rehabilitation treatment on balance in individuals with CANVAS.

The Activities Specific Balance Confidence Scale (ABC) was distributed to individuals with CANVAS during the follow up visit. 30 individuals participated in this study. Participants reported decreased balance confidence across a range of activities. Many participants reported daily (14.1% of participants) or weekly (37.6% of participants) falls and 77.8% of participants indicated the rehabilitation treatment improved their balance.

Results from this study will help to focus future studies to design a specific rehabilitation protocol to better improve balance, reduce falls, and meet the needs of individuals with CANVAS.

GENETIC NEUROPATHIES**Abstract P070 - Cod. 143056****BEYOND NEUROPATHY: AUTONOMIC AND GASTROINTESTINAL RED FLAGS IN ATTR AMYLOIDOSIS**

Gianferrari G.^{*1}, Zucchi E.², Mazzoli M.², Mandrioli J.², Ariatti A.²
¹ *Neuroscience Ph.D. Program, University of Modena and Reggio Emilia, Modena, Italy*, ² *Department of Neurosciences, Azienda Ospedaliero Universitaria di Modena, Modena, Italy*

Hereditary transthyretin amyloidosis (ATTRv) is a progressive multisystem disease in which peripheral neuropathy is a major clinical feature. However, autonomic and gastrointestinal involvement may be prominent, occasionally preceding sensorimotor symptoms and complicating diagnosis

Describe an atypical case of ATTRv amyloidosis presenting with severe autonomic and gastrointestinal manifestations, highlighting their role as early red flags of the disease

A 69-year-old man, with a medical history notable only for bilateral carpal tunnel syndrome, presented with asthenia and muscle atrophy following a two-month history of unexplained hiccups, intractable vomiting, marked weight loss, and alternating hypertensive crises and orthostatic hypotension. Extensive gastroenterological investigations excluded mechanical or neoplastic causes. Family history revealed a father who died of acute myocardial infarction at 84 years and a grandfather who developed progressive limb weakness at 50 years. Neurophysiological studies showed a length-dependent axonal polyneuropathy with acute and chronic denervation, initially raising suspicion of a motor neuron disorder. Recurrent gastrointestinal epi-

sodes compatible with cyclic vomiting followed. Diagnosis was supported by Congo red–positive abdominal fat biopsy and confirmed by genetic testing identifying the pathogenic TTR variant p.Phe84Leu. Cardiac evaluation showed no evidence of overt amyloid cardiomyopathy. Due to severe gastrointestinal involvement, parenteral nutrition was required. Treatment with Vutrisiran, along with symptomatic autonomic and nutritional management, resulted in marked improvement of gastrointestinal symptoms and progressive resumption of oral feeding.

Severe autonomic and gastrointestinal dysfunction may represent early and predominant manifestations of ATTRv neuropathy. Recognition of these atypical features may facilitate earlier diagnosis and timely initiation of disease-modifying therapy

GENETIC NEUROPATHIES**Abstract P072 - Cod. 143518****CHARCOT-MARIE-TOOTH TYPE 2Z WITH ADULT-ONSET RESPIRATORY FAILURE: A CASE REPORT**

Ferullo L.^{*1}, Risi B.¹, Bertella E.¹, Gatta D.¹, Giovanelli G.¹, Poli L.², Padovani A.³, Filosto M.¹

¹ *NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy*, ² *Unit of Neurology, ERN Euro-NMD Center, ASST Spedali Civili, Brescia, Italy*, ³ *Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy*

Pathogenic variants in the Microorchidia CW-type zinc finger 2 (MORC2) gene have been associated with Charcot-Marie-Tooth disease type 2Z (CMT2Z), an autosomal dominant axonal peripheral neuropathy exhibiting marked clinical heterogeneity, ranging from relatively mild disease to severe phenotypes ultimately leading to disability in late adulthood. Respiratory involvement has been occasionally reported but remains poorly characterized, particularly in adult-onset CMT2Z.

We report a 71-year-old male with a long-standing progressive axonal sensorimotor neuropathy clinically consistent with CMT. Clinical history, neurological examination, respiratory function tests, and genetic investigations were performed. Genetic testing, including deletion/duplication analysis and targeted sequencing of PMP22, GJB1, and MPZ genes, yielded negative results. Subsequently, whole-exome sequencing and a multigene virtual panel analysis focusing on hereditary sensorimotor and distal motor neuropathies were conducted. Neurological examination revealed severe tetra paresis with distal predominance, areflexia, muscle hypotonia, and mild impairment of deep sensory modalities. The patient was wheelchair-bound and fully dependent for postural transfers. Mild dysarthria and dysphagia were also observed. Respiratory assessment showed a severe restrictive ventilatory defect (FVC 37%) and ineffective cough, necessitating nocturnal non-invasive ventilation. Exome sequencing identified a heterozygous missense variant, c.1330G > C, p.Gly444Arg, in the MORC2 gene.

The c.1330G > C variant was functionally shown to alter neuronal survival and neurite morphology, consistent with pathogenic MORC2 alleles, supporting its pathogenicity. It was identified in three individu-

als from two families, segregating with autosomal dominant axonal neuropathies with adult-onset proximal motor neuropathy.

Our case highlights the phenotypical heterogeneity of MORC2-related neuropathy and indicates that progressive respiratory failure may occur as an adult-onset manifestation, expanding the spectrum beyond the more commonly reported early-onset phenotypes.

GENETIC NEUROPATHIES

Abstract P074 - Cod. 142966

CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES OF A SINGLE-CENTER COHORT OF PATIENTS WITH CANVAS

Burattini M.^{*}, Girelli F., Caprini C., Conti A., Logullo F.
Neurology Unit - AST Pesaro Urbino, Fano, Italy

Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is an adult-onset, autosomal recessive disorder caused by intronic repeat expansions of the RFC1 gene. The clinical spectrum has broadened, showing variable associations with dysarthria, oscillopsia, dysautonomia, dry spasmodic cough, neuropathic pain and cognitive impairment. Electrodiagnostic studies are fundamental for diagnosis, typically revealing sensory neuronopathy or sensory and motor polyneuropathy.

We retrospectively enrolled all patient with CANVAS identified at the Neurology Unit of AST Pesaro Urbino from January 2022 to January 2026. Assessments included demographic, clinical and electrodiagnostic features.

Out of 5 patients identified, mean age at diagnosis was 63.6 ± 5.9 years with 12.8 ± 6.8 years from first symptoms to diagno-

sis. Gait imbalance and paresthesias were the most common initial manifestations (80%). Three patients (60%) reported a history of dry cough and one (20%) had a family history suggestive of neuropathy. All patients presented with sensory ataxia and two (40%) exhibited also nystagmus and pyramidal signs. No patient displayed the full clinical CANVAS triad at diagnosis. On electroneurography, sensory nerve action potentials were absent bilaterally in all but one patient, in whom they were severely reduced. Motor nerve conduction studies were normal in all subjects.

Our study highlights the wide clinical spectrum of CANVAS presentation, where electrophysiological testing is crucial identifying sensory neuronopathy. A thorough clinical and electrophysiological evaluation, followed by prompt genetic testing, is key to diagnosing unexplained sensory neuronopathy, especially when associated with chronic cough and mixed ataxia.

GENETIC NEUROPATHIES

Abstract P076 - Cod. 142671

CLINICAL PROFILE OF F64L ATTRV PATIENTS: EVIDENCE FROM A MULTICENTER ITALIAN STUDY

Ceccanti M.^{*7}, Guaraldi P.², Romano A.³, Antonini G.¹, Barilaro A.⁴, Briani C.⁵, Burattini M.⁶, Gianoli M.², Carlini G.⁸, Cianci V.⁹, Currò Dossi M.¹⁰, Di Lisi D.¹¹, Di Muzio A.¹², Ratti A.¹³, Filosto M.¹⁴, Gasverde S.¹⁵, Gemelli C.¹⁶, Gentile L.¹⁷, Goglia M.¹⁸, Leonardi L.¹⁹, Longhi S.²⁰, Lotti A.⁴, Manganelli F.²¹, Mazzeo A.¹⁷, Augello S.M.¹⁷, Milella G.²², Novo G.¹¹, Fenu S.²³, Palumbo G.²¹, Petrelli C.²⁴, Poli L.²⁵, Pradotto L.G.²⁶, Russo M.¹⁷, Salvalaggio A.⁵, Falzone Y.¹³, Sciarrone M.A.²⁷, Sellitti L.²⁸, Tagliapietra M.²⁹, Tozza S.²¹,

Table 1: Nerve conduction studies. Data are expressed in medians with interquartile ranges. CMAP: compound muscle action potential.

Motor nerve conduction studies				
Nerve	CMAP amplitude (mV)	Distal motor latency (ms)	Velocity (m/s)	F-wave latency (ms)
Median	10,4 (10,0-12,0)	3,6 (3,1-3,7)	50,0 (50,0-52,0)	32,1 (28,7-32,5)
Ulnar	11,5 (10,3-12,8)	2,3 (2,2-2,4)	56,5 (54,8-58,3)	29,9 (28,1-31,6)
Fibular	6,0 (5,2-6,6)	4,5 (4,2-5,0)	42,0 (40,0-45,0)	54,0 (50,5-55,0)

Sensory nerve conduction studies		
Nerve	Sensory amplitude (uV)	Velocity (m/s)
Median	0 (0-5)	0 (0-50)
Ulnar	0 (0-7)	0 (0-52)
Radial	2,5 (0-7,5)	0 (0-53)
Lateral antebrachial cutaneous	0 (0-0)	0 (0-0)
Medial antebrachial cutaneous	0 (0-0)	0 (0-0)
Sural	0 (0-0)	0 (0-0)
Superficial fibular	0 (0-0)	0 (0-0)

Castiglia M.²¹, Turri M.³⁰, Verriello L.³¹, Chimenti C.³², Vitali F.²⁷, Brighina F.³³, Rini N.³³, Inghilleri M.³⁴, D'Angelo R.², Cambieri C.¹, Libonati L.¹, Pareyson D.²³, Moret F.¹, Luigetti M.³⁵, Di Stefano V.³³
¹ Sapienza University of Rome, Rome, Italy, ² IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ⁴ AOU Careggi and Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy, ⁵ Neurology Unit, Department of Neuroscience, University of Padua, Padua, Italy, ⁶ Neurology Unit, Ospedale Santa Croce di Fano, Fano, Italy, ⁷ Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, ⁸ Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy, ⁹ Neurology Unit, Great Metropolitan Hospital "Bianchi Melacrino Morelli", Reggio Calabria, Italy, ¹⁰ Department of Neurology, Santa Maria delle Croci Hospital, Ravenna, Italy, ¹¹ Division of Cardiology, University Hospital Paolo Giaccone, Palermo, Italy, ¹² Department of Neuroscience, Imaging and Clinical Sciences, "G. D'Annunzio" University, Chieti, Italy, ¹³ Division of Neuroscience, Department of Neurology, Institute of Experimental Neurology, San Raffaele Scientific Institute, Milano, Italy, ¹⁴ Department of Clinical and Experimental Sciences, University of Brescia and NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ¹⁵ ASL TO4, Ciriè, Italy, ¹⁶ IRCCS Ospedale Policlinico San Martino, Genoa, Italy, ¹⁷ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ¹⁸ Neuromuscular Diseases Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ¹⁹ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ²⁰ Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy, ²¹ Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples 'Federico II', Naples, Italy, ²² Neurology Unit, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari Aldo Moro, Bari, Italy, ²³ S.C. Malattie Neurologiche Rare, Dipartimento di Neuroscienze Cliniche, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ²⁴ Neurology Unit, AV3, ASUR Marche, Macerata, Italy, ²⁵ Unit of Neurology, ASST Spedali Civili, Brescia, Italy, ²⁶ Department of Neuroscience "Rita Levi Montalcini", University of Turin And 28IRCCS Istituto Auxologico Italiano, Piancavallo (Vb), Turin and Milan, Italy, ²⁷ Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ²⁸ IRCCS Istituto Auxologico Italiano, Piancavallo (Vb), Milano, Italy, ²⁹ Department of Neuroscience, Biomedicina e Movimento,

Università di Verona, Verona, Italy, ³⁰ Dipartimento di Neurologia/Stroke Unit, Ospedale di Bolzano, Bolzano, Italy, ³¹ Neurology Unit, Department of Neurosciences, University Hospital Santa Maria della Misericordia, Udine, Italy, ³² Department of Internal Clinical, Anesthesiological and Cardiovascular Sciences, "Sapienza" University of Rome, Rome, Italy, ³³ Department of Biomedicine, Neuroscience and Advanced Diagnostics (BIND), University of Palermo, Palermo, Italy, ³⁴ Department of Human Neuroscience, Sapienza University of Rome And IRCCS Neuromed, Rome and Pozzilli, Italy, ³⁵ Dipartimento di Neuroscienze, Organi di Senso e Torace, UOC Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS And Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy

The F64L variant is one of the most prevalent TTR mutations in Italy and is typically associated with a mainly neurologic phenotype with limited cardiac involvement.

We analyzed data from 181 ATTRv patients included in the multi-center PatisiranItaly registry and treated with patisiran since 2020. Neurological impairment scores, Norfolk QoL-DN, and cardiac parameters were compared among F64L (n = 54), V30M (n = 37), and non-F64L (n = 125) patients at baseline and during follow-up. Cluster analysis was performed to identify patient subgroups based on these variables.

F64L accounted for 30.9% of the cohort. Compared with non-F64L patients, those carrying the F64L variant showed a higher prevalence of neurological onset and phenotype, thinner interventricular septum, and lower NT-proBNP levels. Cluster analysis identified two distinct groups, largely reflecting F64L versus non-F64L status and associated neurological severity. F64L patients exhibited milder cardiac involvement compared with V30M patients. Longitudinal repeated-measures ANOVA demonstrated stable clinical and instrumental parameters over time.

The F64L variant is characterized by predominant neurological involvement and less severe cardiac involvement. Mutation-specific diagnostic and follow-up strategies are therefore crucial to accurately capture its natural history and treatment response

F64L prevalence in Italy



Region of residence	ATTRv F64L Patisiran-treated patients (n.)	Frequency (%)	Prevalence/million residents
Sicily	27	50.0	5.63
Calabria	6	11.1	3.26
Abruzzo	2	3.7	1.58
Campania	8	14.8	1.43
Trentino-Alto Adige	1	1.9	0.92
Lazio	5	9.3	0.88
Liguria	1	1.9	0.66
Puglia	1	1.9	0.26
Emilia-Romagna	1	1.9	0.22
Veneto	1	1.9	0.21
Lombardy	1	1.9	0.10
Total	54	100.0	1.23

GENETIC NEUROPATHIES

Abstract P078 - Cod. 143252

DESIGN AND RATIONALE OF TRITON-PN, A PHASE 3 STUDY TO EVALUATE THE EFFICACY OF NUCRESIRAN IN PATIENTS WITH TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY

Luigetti M.*¹, Obici L.P.², Cárdenas--Soto K.³, Waddington--Cruz M.⁴, Plante--Bordeneuve V.⁵, Losada I.⁶, Brannagan T.⁷, Gillmore J.⁸, Berk J.⁹, Li J.¹⁰, Lau K.H.V.¹⁰, Gonzalez--Duarte A.¹¹

¹ Fondazione Policlinico Universitario A. Gemelli. UOC Neurologia., Roma, Italy, ² Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy, ³ "Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico, ⁴ Hospital Universitário Clementino Fraga Filho, Centro de Estudos em Paramiloidose Antônio Rodrigues de Mello, Universidade Federal do Rio de Janeiro., Rio de Janeiro, Brazil, ⁵ Neurology - Amyloid Network, CHU Henri Mondor, APHP, University Paris Est - Créteil, Créteil, France, ⁶ Hospital Universitario Son Llatzer, Instituto de Investigación Sanitaria Illes Balears, Palma de Mallorca, Spain, ⁷ "Columbia University, New York, United States of America, ⁸ National Amyloidosis Centre, University College London, Royal Free Hospital, London, United Kingdom, ⁹ "Boston University School of Medicine, Boston, United States of America, ¹⁰ Alnylam Pharmaceuticals, Cambridge, United States of America, ¹¹ NYU School of Medicine, New York, United States of America

ATTRv-PN is a progressive, fatal disease caused by misfolded transthyretin depositing as amyloid fibrils in nerves. RNA interference (RNAi) therapeutics like patisiran and vutrisiran, approved to treat ATTRv-PN, suppress hepatic transthyretin production; therapies with greater, more consistent transthyretin reduction may improve outcomes. RNAi therapy nucresiran(ALN-TTRsc04) may offer this advantage.

Describe the rationale and design of TRITON-PN, a phase 3, global, open-label, randomized study, evaluating the efficacy and safety of nucresiran in patients with ATTRv-PN.

TRITON-PN will enroll ~125 patients with ATTRv-PN. Inclusion criteria include: age 18–85 years, ATTRv-PN diagnosis with documented pathogenic TTR variant, NIS 5–130, PND ≤IIIb, and KPS ≥60%. Patients with NYHA Class > II or prior TTR silencer use will be excluded. Patients will be randomized(4:1) to 300 mg subcutaneous nucresiran every 6months or 25 mg subcutaneous vutrisiran every 3months. The historical, external placebo group from the patisiran APOLLO study will serve as the control for the primary and secondary clinical endpoints. The primary endpoint is change from baseline in modified NIS+7 at Month 9. Secondary endpoints include change from baseline at Months 9 and 18 in Norfolk QoL-Diabetic Neuropathy Questionnaire and mBMI. RODS, 10-MWT, and modified NIS+7 will be assessed at Month 18. Serum TTR knockdown will be compared with in-study vutrisiran-treated patients.

TRITON-PN will assess the effects of nucresiran on disease-related measures in patients with ATTRv-PN. Nucresiran may provide greater clinical benefits and reduced treatment burden versus current RNAi therapeutics through deeper, more sustained transthyretin knockdown, lower interpatient variability, and less frequent dosing.

GENETIC NEUROPATHIES

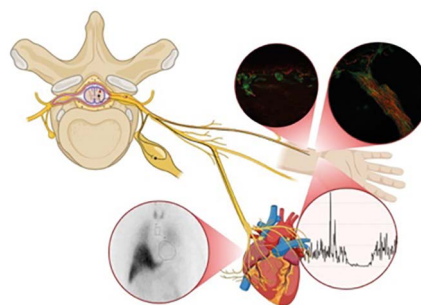
Abstract P080 - Cod. 142675

EARLY SMALL FIBER INVOLVEMENT IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: A MULTIMODAL STUDY COMBINING ¹²³I-MIBG, SKIN BIOPSY, AND NEUROPHYSIOLOGY

Frantellizzi V.¹, Cambieri C.², Galosi E.², Chimenti C.³, Marchionni G.³, Alfarano M.³, Ballatore F.³, Costantino J.³, Luigetti M.⁴, Sciarrone M.A.⁵, Graziani F.⁶, Leonardi L.⁷, Musumeci B.⁸, Libonati L.², Moret F.², Di Giulio M.², Garibaldi M.⁹, Forcina F.⁹, Truini A.², De Feo M.S.¹, De Vincentis G.¹, Inghilleri M.¹⁰, Ceccanti M.*²

¹ Department of Radiological Sciences, Oncology and Anatomy Pathology, Sapienza University of Rome, Rome, Italy, ² Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, ³ Department of Medical and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy, ⁴ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore And Dipartimento di Neuroscienze, Organi di Senso e Torace, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ⁵ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Rome, Italy, ⁶ Dipartimento di Scienze Cardiovascolari-CUORE Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, ⁷ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ⁸ Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy, ⁹ Department of Neurology, Mental Health and Sensory Organs (NESMOS), Sapienza University of Rome, Rome, Italy, ¹⁰ Department of Human Neuroscience, Sapienza University of Rome And IRCCS Neuromed, Rome and Pozzilli, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a multisystem disorder characterized by progressive involvement of the peripheral nervous system and the heart. Early detection of subclinical organ involvement remains challenging. This study aimed to investigate cardiac sympathetic innervation and small fiber dysfunction using a multimodal approach combining ¹²³I-metaiodobenzylguanidine (¹²³I-mIBG) scintigraphy, skin biopsy, and cutaneous silent period (CSP) assessment in symptomatic patients and asymptomatic carriers (AC). In this cross-sectional study, 14 symptomatic ATTRv patients, 18 AC, and 32 healthy controls (HC) underwent ¹²³I-mIBG imaging to assess early and late heart-to-mediastinum ratios (e-H/M, I-H/M) and summed scores (ESS, LSS). Skin biopsies were performed to quantify intraepidermal nerve fiber density (IENFD) and piloerector



muscle nerve fiber density (PMNFD) in proximal and distal sites. CSP testing was used to evaluate A-δ fiber function. In AC, correlations between ¹²³I-MIBG parameters and time from predicted disease onset (Δ-PADO) were analyzed.

Late H/M ratios were significantly reduced in AC compared with HC (1.73 ± 0.23 vs 1.94 ± 0.19 ; $p < 0.05$) and further decreased in symptomatic patients (1.37 ± 0.25 ; $p < 0.01$). Δ-PADO correlated with e-H/M ($p < 0.05$), ESS ($p < 0.01$), and LSS ($p < 0.01$). Reduced IENFD in the lower limbs was observed in approximately half of AC. CSP latencies were prolonged or absent in patients with more advanced disease.

A multimodal approach integrating ¹²³I-MIBG scintigraphy, skin biopsy, and CSP reveals early cardiac sympathetic denervation and small fiber involvement in ATTRv, even in asymptomatic carriers. This combined strategy may improve early detection, risk stratification, and monitoring of disease progression in ATTRv.

GENETIC NEUROPATHIES

Abstract P082 - Cod. 143466

EXPLORING PHENOTYPIC HETEROGENEITY OF RARE MFN2 VARIANTS IN THE GENERAL POPULATION: INSIGHTS FROM THE UK BIOBANK COHORT

Gagliardi D.^{*1}, Vilella C.¹, Sebastiani E.¹, Corti S.², Comi G.P.², Houlden H.³, Tucci A.⁴, Ronchi D.²

¹ Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy, ² Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), Università degli Studi di Milano, Milano, Italy, ³ Department of Neuromuscular Diseases, Institute of Neurology, University College London, London, United Kingdom, ⁴ William Harvey Research Institute, Queen Mary University of London, London, United Kingdom

Pathogenic heterozygous MFN2 variants cause hereditary neuropathies, including CMT2A and HMSN VIA, accounting for 4-7% of genetically diagnosed CMTs. Biallelic defects are associated with heterogeneous phenotypes, such as multiple symmetric lipomatosis, with or without peripheral neuropathy and paediatric mtDNA depletion syndrome. Recently, MFN2 variants have also been linked to amyotrophic lateral sclerosis with or without frontotemporal dementia, and reported in a patient affected by distal myopathy.

Here, we aim to leverage the UK Biobank (UKB) cohort to assess the frequency of pathogenic (P), likely pathogenic (LP) and variants of uncertain significance (VUS) in MFN2 and to evaluate genotype-phenotype correlations. We analysed rare (MAF < 0.001) variants in the MFN2 gene within exome sequencing data from 470,000 individuals over 40 years old at the time of recruitment. We evaluated their pathogenic role using referenced databases and according to ACMG guidelines. Demographic features and health outcomes were collected for carriers of MFN2 variants and compared with those from non-carriers.

We identified 509 rare variants (116 P and LP, and 393 VUS) across 2,889 individuals, 159 of which have been already reported in literature. The frequency of known pathogenic MFN2 variants is 1:745 in

UKB, raising up to 1:578 when considering also previously unreported variants. However, only 2.2% of them presented with neuropathy. MFN2 carriers have higher odds of having glaucoma compared to non-carriers. Further association analyses are ongoing.

Overall, these findings suggest that MFN2 variants are more frequent than clinically expected and likely underrecognized, possibly due to heterogeneous and non-neurologic clinical presentations.

GENETIC NEUROPATHIES

Abstract P084 - Cod. 143408

HIGH DIAGNOSTIC YIELD OF CLINICAL EXOME SEQUENCING IN A COHORT OF PATIENTS AFFECTED WITH HEREDITARY PERIPHERAL NEUROPATHY

Velardo D.^{*1}, Moliterno N.², Abati E.², Gagliardi D.², Magri F.¹, Ravaglia S.³, Del Bo R.⁴, Bestetti I.⁵, Finelli P.⁵, Corti S.⁴, Comi G.P.⁴, Ronchi D.⁴

¹ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular and Rare Disease Unit, Milan, Italy, ² IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy, ³ IRCCS Foundation Mondino National Neurological Institute, Neuromuscular Unit, Pavia, Italy, ⁴ Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, ⁵ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Medical Genetics Laboratory, Milan, Italy

Hereditary peripheral neuropathy (HPN) encompasses a group of neurological disorders displaying wide-ranging symptoms, clinical severity, and causes. More than 150 genes have been implicated in HPN: some of them (i.e. PMP22, MPZ, GJB1) occurring with high frequency across international cohorts of patients while others are rarely identified or display regional selectivity.

The achievement of a reliable molecular diagnosis can improve clinical management, provide appropriate genetic counseling and enable potential therapeutic options.

We present a cohort of 48 patients with suspected hereditary peripheral neuropathy undergoing NGS-based molecular testing in our Center. Our approach includes clinical exome sequencing filtered for HPN-related genes including Copy Number Variation (CNV) analysis for the detection of gene deletions and duplications. Sanger sequencing and/or MLPA analysis are used for validation studies in the probands and their relatives. A definitive diagnosis (conclusive molecular findings was obtained in 19 subjects (40%) with PMP22 being positive in 9 subjects (6 duplication and 3 deletion) followed by biallelic variants in SORD (3 subjects). Molecular defects in rare genetic forms (KIF5A, FBLN5, DHTKD1, POLR3A, NEFL, TRPV4, KIF21A) contributed to definitive or probable diagnosis in 7 additional probands. Overall, a positive genetic report was obtained in 23/48 subjects (48% of the cohort). We also identified some subjects with pathogenic or biallelic VUS in genes not classically related with HPN (i.e. MICU1, TBK1): these molecular defects are currently under evaluation.

Clinical exome sequencing coupled with CNV analysis is a versatile approach to face the complexity of HNP genetics.

GENETIC NEUROPATHIES

Abstract P086 - Cod. 142962

IS SUDOSCAN A RELIABLE MARKER OF DISEASE PROGRESSION IN HATTR?

Portera V.*, Alonge P., Messina C., Sgaraglino A., Campo S., Di Stefano V., Brighina F.

Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.) - University of Palermo, Palermo, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a common genetic cause of polyneuropathy, resulting from mutations in the TTR gene. The disease is multisystemic, affecting cardiovascular, sensorimotor, and autonomic functions. Sudoscan is a rapid, non-invasive tool measuring electrochemical skin conductance (ESC) to assess autonomic dysfunction, but its utility remains unclear. This study aimed to evaluate Sudoscan's role in the follow-up of patients treated with

vutrisiran, a TTR silencer approved for ATTRv polyneuropathy.

patients were evaluated at baseline and after 9 months of vutrisiran therapy. Assessments included Karnofsky Performance Status (KPS), Composite Autonomic Symptom Score-31 (COMPASS-31), Compound Autonomic Dysfunction Test (CADT), nerve conduction studies, and Sudoscan. Wilcoxon signed-rank tests evaluated changes in scores, and Kendall's tau was applied to assess correlations between scores and percentage diminution of ESC and other clinical measures.

Twenty-five consecutive patients (14 women, 11 men; 53–88 years, mean 69.7 ± 8.2) were enrolled. At baseline, ESC was pathological in 12 patients (48%), suggesting autonomic neuropathy. After 9 months, ESC showed a non-significant improvement in the upper limbs, while lower limb results remained stable. COMPASS-31 scores showed a trend toward worsening ($p = 0.13$, one-tailed). ESC values did not correlate with other clinical scores at baseline or follow-up; similarly, the percentage diminution of ESC was not correlated with changes in clinical or neurophysiological scores.

Correlazioni

			delta mani	delta piedi	CADT delta	Karnofsky delta	Compass delta
Tau_b di Kendall	delta mani	Coefficiente di correlazione	1,000	,258	-,269	-,319	,074
		Sig. (a due code)	.	,138	,139	,093	,675
		N	18	18	18	18	18
	delta piedi	Coefficiente di correlazione	,258	1,000	-,183	-,201	,007
		Sig. (a due code)	,138	.	,312	,287	,970
		N	18	18	18	18	18
	CADT delta	Coefficiente di correlazione	-,269	-,183	1,000	,099	-,337
		Sig. (a due code)	,139	,312	.	,615	,067
		N	18	18	18	18	18
	Karnofsky delta	Coefficiente di correlazione	-,319	-,201	,099	1,000	-,442*
		Sig. (a due code)	,093	,287	,615	.	,021
		N	18	18	18	18	18
	Compass delta	Coefficiente di correlazione	,074	,007	-,337	-,442*	1,000
		Sig. (a due code)	,675	,970	,067	,021	.
		N	18	18	18	18	18
Rho di Spearman	delta mani	Coefficiente di correlazione	1,000	,359	-,356	-,381	,081
		Sig. (a due code)	.	,143	,147	,119	,749
		N	18	18	18	18	18
	delta piedi	Coefficiente di correlazione	,359	1,000	-,265	-,223	-,004
		Sig. (a due code)	,143	.	,288	,374	,989
		N	18	18	18	18	18
	CADT delta	Coefficiente di correlazione	-,356	-,265	1,000	,123	-,440
		Sig. (a due code)	,147	,288	.	,627	,068
		N	18	18	18	18	18
	Karnofsky delta	Coefficiente di correlazione	-,381	-,223	,123	1,000	-,535*
		Sig. (a due code)	,119	,374	,627	.	,022
		N	18	18	18	18	18
	Compass delta	Coefficiente di correlazione	,081	-,004	-,440	-,535*	1,000
		Sig. (a due code)	,749	,989	,068	,022	.
		N	18	18	18	18	18

*. La correlazione è significativa a livello 0,05 (a due code).

Sudoscan offers a fast, non-invasive method for detecting autonomic neuropathy, but it doesn't reliably track progression in late-onset ATTRv patients. Clinical assessments remain essential, and Sudoscan's role may be limited to initial screening rather than longitudinal monitoring.

GENETIC NEUROPATHIES

Abstract P088 - Cod. 142990

LONG TERM REAL-LIFE WITH VUTRISIRAN IN ATTRV AMYLOIDOSIS: A SINGLE CENTER EXPERIENCE

Portera V.*, Alonge P., Messina C., Sgaraglino A., Campo S., Di Stefano V., Brighina F.

Department of Biomedicine, Neuroscience and Advanced Diagnostics (Bi.N.D.), University of Palermo, Palermo, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a common genetic cause of polyneuropathy, resulting from mutations in the TTR gene. Vutrisiran is the most recently approved TTR silencer for the treatment of ATTRv. The aim of this study is to evaluate the efficacy and safety of vutrisiran in a real-world, single-centre cohort of Sicilian ATTRv patients.

Patients were clinically assessed before starting vutrisiran therapy (T0) and after 9 (T9) and 18 (T18) months of follow-up. Evaluations

included the 6-Minute Walk Test (6MWT), body mass index, CADT, COMPASS, FAP stage, Karnofsky Performance Status, Neuropathy Impairment Score (NIS Total and NIS Weakness), and Norfolk Quality of Life-Diabetic Neuropathy questionnaire. Changes between baseline and follow-up were analysed using paired-sample t-tests.

Twenty-four consecutive patients [VP1.1](13 women, 11 men; age range 53-88 years, mean 69.5 ± 8.2) were enrolled. Eighteen patients (75%) completed 9 months of treatment and eight (33.3%) completed 18 months. Median follow-up was 9 months (range 0-18). No statistically significant differences were observed at T9; however, a trend towards improvement was noted in Karnofsky Performance Status and COMPASS scores, while slight, worsening was observed in 6MWT and FAP stage. At 18 months, 3/8 patients showed mild improvement in 6MWT and Karnofsky scores compared to baseline, and only one patient progressed from FAP stage 1 to stage 2. Only three patients experienced mild systemic adverse events, without reports of injection-site reactions.

Vutrisiran confirms itself as a safety medication and a stabilizer of the clinical picture.

GENETIC NEUROPATHIES

Abstract P090 - Cod. 143091

MOTOR, EXTRAPYRAMIDAL, AND COGNITIVE

	N1	N2	N3	N4	N5	N6	N7	N8
NIS Total T0	5	30	28	32	11	123	4	2
NIS Total T9	2	70	28	2	24	79,5	15	12
NIS Total T18	10	37	23	17	48	85,5	10	27
NIS weakness T0	0	12	12	32	2	83	29	9
NIS weakness T9	0	38	12	0	17	51,5	8	6
NIS weakness T18	3	12	5	2	43	56,5	10	10
Norfolks T0	0	69	46	30	46	57	18	22
Norfolks T9	14	75	34	30	33	64	6	25
Norfolks T18	69	76	30	36	41	83	23	6
CADT T0	18	4	13	14	13	18	14	13
CADT T9	13	4	14	14	13	18	12	13
CADT T18	11	10	13	12	18	16	18	16
KarnofskyT0	90	50	80	80	80	50	90	80
KarnofskyT9	90	50	80	70	80	40	90	80
Karnofsky T18	90	50	90	80	90	50	80	60
Compass T0	9	25	22	9	22	10	14	18
Compass T9	19	18	20	19	18	13	13	19
Compass T18	19	18	20	19	18	13	31	24
FAP T0	1	2	1	1	1	1	1	1
FAP T9	1	2	1	1	1	2	1	1
FAP T18	1	2	1	1	1	2	1	1
BMI T0	26,59574	18,35938	20,71569	23,23346	24	31,2213	34,72	40,09
BMI T9	28,29335	18,35938	20,38157	23,23346	24	30,85399	34,24	40,59
BMI T18	30,18959	17,84652	20,04745	23,63403	24	30,11621	32,44	38,8
6MWT T0	400	40	470	320	280	250	360	235
6MWT T9	400	40	450	310	280	300	340	210
6MWT T18	382,5	630		360	345	330	435	435

INVOLVEMENT IN RFC1 DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Benvenuto G.^{*1}, Massucco S.¹, Hamedani M.¹, Ponzano M.², Manca R.³, Roveta E.⁴, Pichiecchio A.⁵, Asteggiano C.⁵, Zaottini F.⁴, Maria João M.⁶, Currò R.⁷, Garnerò M.⁴, Gemelli C.⁴, Trigiante M.¹, Vollaro A.F.M.¹, Barone C.¹, Bavestrello G.¹, Pardini M.¹, Schenone A.¹, Massa F.¹, Cortese A.⁷, Grandis M.¹

¹ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI), University of Genoa, Largo Paolo Daneo 3, 16132, Genova, Italy, Genova, Italy, ² Department of Health Sciences, Section of Biostatistics, University of Genoa, Genova, Italy, Genova, Italy, ³ Department of Medicine and Surgery, University of Parma, Via Volturno 39, 43125 Parma, Italy, Parma, Italy, ⁴ IRCCS Azienda Ospedaliera Metropolitana Policlinico San Martino, Largo Rosanna Benzi 10, 16132, Genova, Italy, Genova, Italy, ⁵ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, Pavia, Italy, ⁶ Department of Neurology, Unidade Local de Saúde de Gaia/Espinho, 4434-502 Porto, Portugal, Porto, Portugal, ⁷ Department of Neuromuscular Disease, UCL Queen Square Institute of Neurology, London, United Kingdom, London, United Kingdom

Biallelic intronic repeat expansions in RFC1 are a major genetic cause of cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS), with expanding phenotypic heterogeneity.

To assess the prevalence and clinical correlates of motor neuron, extrapyramidal, and cognitive involvement in RFC1-related disease through a systematic review and meta-analysis. PubMed, Scopus, and Web of Science were searched to March 2025 for studies reporting these features in genetically confirmed cases. Study-level and individual participant data (IPD) on demographics and neurological features were collected. Random-effects models estimated pooled prevalences (95% CI), and mixed-effects logistic regression explored associations accounting for within-study clustering.

Thirty-seven studies met inclusion criteria; 36 (874 patients) were included in proportion meta-analyses. IPD meta-analysis involved 312 patients (mean age 66.9 ± 10.8 years; median disease duration 12 [IQR 7–18] years; 51.5% male). Upper and lower motor neuron signs were present in 18% (95% CI 6–34%) and 11% (95% CI 2–24%), respectively. ACAGG repeat expansions were associated with increased odds of muscle atrophy (OR 17.90, $p < 0.001$) and weakness (OR 11.69, $p < 0.001$); male sex was independently associated with atrophy (OR 2.71, $p = 0.038$). Parkinsonism and cognitive impairment showed pooled prevalences of 8% (95% CI 1–18%) and 31% (95% CI 13–53%), with predominant executive–attentional deficits. Cognitive impairment correlated with longer disease duration (OR 1.04, $p = 0.047$) and was more frequent among biallelic AAGGG carriers.

Motor neuron, extrapyramidal, and cognitive manifestations expand the clinical spectrum of RFC1-related disease. Prevalence estimates remain limited by inter-study heterogeneity and potential publication bias. Large, multicenter cohorts with standardized phenotyping are warranted to clarify their clinical significance.

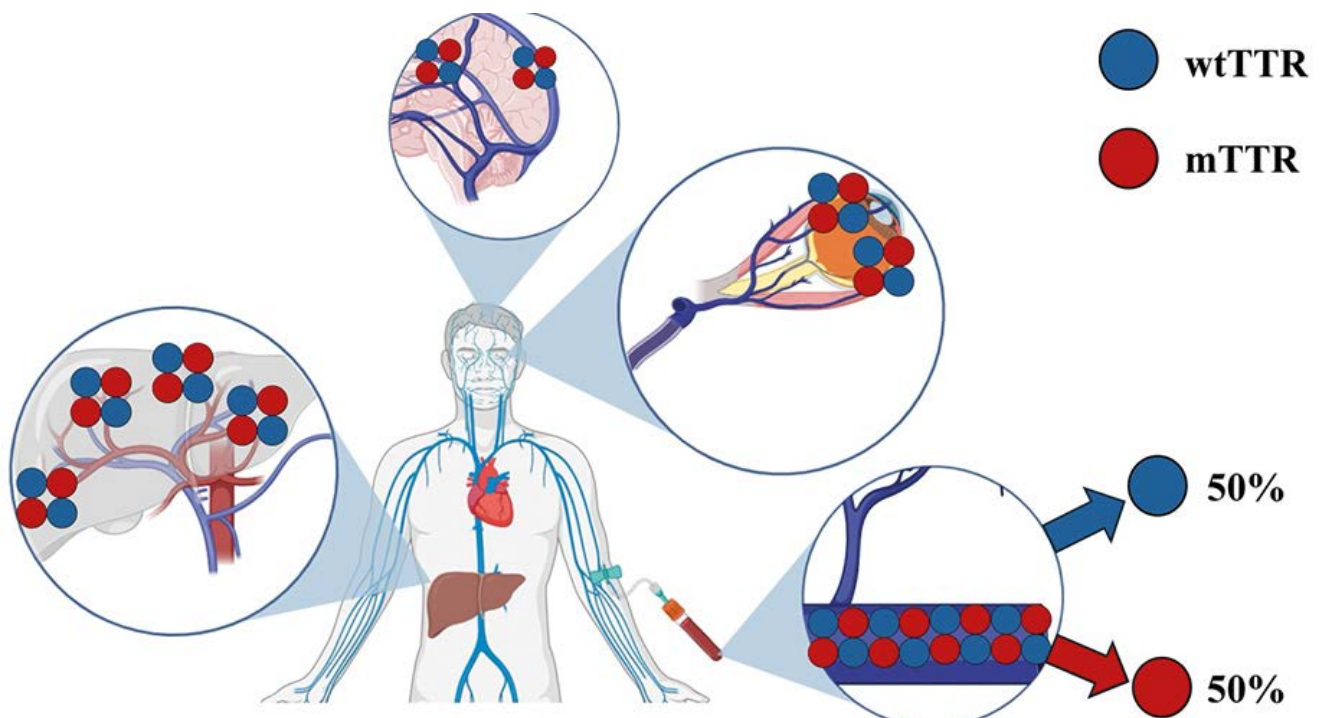
GENETIC NEUROPATHIES

Abstract P092 - Cod. 142678

MULTICENTER STUDY PROPOSAL TO QUANTIFY HEPATIC AND EXTRAHEPATIC TTR SYNTHESIS IN LIVER-TRANSPLANTED ATTRV PATIENTS USING MASS SPECTROMETRY

Ceccanti M.^{*1}, Cambieri C.¹, Libonati L.¹, Moret F.¹, Leonardi L.², Luigetti M.³, Inghilleri M.⁴

¹ Department of Human Neuroscience, Sapienza University of Rome,



Rome, Italy, ² Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, Rome, Italy, ³ Dipartimento di Neuroscienze, Organi di Senso e Torace, UOC Neurologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS And Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ⁴ Department of Human Neuroscience, Sapienza University of Rome And IRCCS Neuromed, Rome and Pozzilli, Italy

Hereditary transthyretin amyloidosis (ATTRv) is caused by deposition of misfolded transthyretin (TTR). Although it is often assumed that ~95% of circulating TTR is liver-derived, this estimate lacks experimental confirmation. Liver transplantation, previously the only disease-modifying therapy, replaces hepatic mutant TTR with wild-type (wt) protein, while extrahepatic tissues, such as retinal pigment epithelium and choroid plexus, continue to produce mutant TTR. This model provides a unique opportunity to study hepatic versus extrahepatic TTR synthesis.

This multicenter study will include ATTRv patients who underwent liver transplantation and are treated with TTR synthesis inhibitors. Mass spectrometry will be used to distinguish wt from mutant TTR and quantify their relative proportions in biological samples. This approach will estimate the fraction of TTR from hepatic synthesis (expected 100% wt) versus extrahepatic synthesis (expected 50% wt, 50% mutant). Treatment with TTR synthesis inhibitors, which selectively suppress hepatic TTR production, will allow assessment of the degree of hepatic inhibition and residual extrahepatic synthesis. Liver-transplanted patients are expected to show predominantly wt TTR, with a measurable residual fraction of mutant TTR reflecting ongoing extrahepatic production. Mass spectrometry is anticipated to discriminate and quantify both TTR forms reliably. TTR synthesis inhibitors are expected to reduce hepatic TTR, allowing indirect estimation of hepatic inhibition and the proportional contribution of extrahepatic synthesis.

This study will provide the first experimental estimation of hepatic versus extrahepatic TTR-synthesis in ATTRv. A multicenter design is essential to achieve a sufficient sample size. Findings are expected to improve understanding of mechanisms underlying therapeutic response in ATTRv

GENETIC NEUROPATHIES

Abstract P094 - Cod. 143521

OPHTHALMOLOGICAL INVOLVEMENT IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: A MULTIMODAL EVALUATION

Cerantola E.^{*1}, Frizziero L.², Cipriani A.³, De Michieli L.³, Tiero B.¹, Midena E.², Salvalaggio A.¹, Briani C.¹

¹ Neurology Unit, Department of Neuroscience, University of Padova, Padova, Italy, ² Ophthalmology Unit, Department of Neuroscience, University of Padova, Padova, Italy, ³ Department of Cardiac Thoracic and Vascular Sciences and Public Health, University of Padova, Padova, Italy

Hereditary transthyretin amyloidosis (ATTRv) exhibits high phenotypic variability. Ophthalmological involvement is likely underestimated and may progress despite gene-silencing therapy.

Twelve ATTRv patients (9 different mutations, aged 67.8±13.8 years,

disease duration 3.25±1.54 years, therapy duration 12.42±8.5 months) underwent neurological, cardiac, and ophthalmological evaluation, including optical coherence tomography (OCT), OCT-angiography (OCTA), and corneal confocal microscopy (CCM). Post-hoc analysis compared longer- versus shorter-treated patients (23±5 vs 1.8±5.8 months).

All patients had neuropathy (median NIS 15, 1–113.75; 10/12 FAP stage 1, 2/12 stage 2). Visual acuity was generally preserved (median 85 ETDRS, 74–85). Cataract occurred in 10/24 eyes, vitreous opacities in 2/12 patients, conjunctival vascular tortuosity in 3/12, and dry eyes in 2/12. CCM revealed alterations in 6/10 patients and corneal deposits in 6/11. Retinal pigment epithelium abnormalities were identified in 6/24 eyes. OCT was largely normal; longer-treated patients showed thinner peripapillary retinal nerve fiber layer, particularly in nasal sectors and papillomacular bundles. CCM and OCTA metrics were lower in patients versus controls, and did not correlate with disease duration or age. Longer-treated patients had reduced corneal nerve fiber density and length but increased branching on CCM, and reduced vessel coverage and length in the nerve fiber layer plexus on OCTA.

Ophthalmological involvement was common, heterogeneous, and often subclinical. Consistent findings included corneal nerve alterations, deposits, and retinal microvascular changes. Ocular progression appeared to continue despite systemic therapy, likely due to limited ocular penetration of gene-silencing treatments. Multimodal imaging enables early detection, highlighting the need for longitudinal ophthalmological monitoring even in treated patients.

GENETIC NEUROPATHIES

Abstract P096 - Cod. 142617

P. HIS110ASN: CONFIRMATION OF PATHOLOGICAL ATTRV VARIANT

Sciarrone M.A.^{*1}, Vitali F.¹, Meucci M.C.², Graziani F.², Luigetti M.¹
¹ UOC Neurologia, Fondazione Policlinico Universitario Agostino Gemelli-IRCCS, Rome, Italy, ² Dipartimento di Scienze Cardiovascolari-CUORE, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a multisystemic disorder caused by pathogenic variants in the transthyretin (TTR) gene, although variants of uncertain significance (VUS) may complicate diagnosis and management.

We report the case of a 79-year-old man admitted for acute heart failure who was found to have cardiac amyloidosis. Clinical, electrocardiographic and echocardiographic red flags prompted bone-tracer cardiac scintigraphy, which demonstrated intense myocardial uptake consistent with transthyretin amyloid cardiomyopathy. Genetic testing revealed a heterozygous p.His110Asn TTR variant, classified as a VUS.

Neurological assessment disclosed mild sensory and autonomic neuropathy, supported by neurophysiological studies. Given the uncertain pathogenicity of the variant, a sural nerve biopsy was performed, revealing severe fibre loss and Congo red–positive amyloid deposits, thereby establishing a causal link between the mutation and the clinical phenotype. These findings supported initiation of gene-silencing

therapy. Genetic screening of the patient's son identified the same variant, associated with mild autonomic symptoms but no cardiac involvement, and prompted clinical surveillance.

This case highlights the phenotypic heterogeneity associated with the p.His110Asn TTR variant and supports its potential pathogenic role in ATTRv with mixed cardiac and neurological involvement. It underscores the importance of comprehensive clinical evaluation and, in selected atypical cases, the continued diagnostic value of nerve biopsy to guide therapeutic decisions. Longitudinal follow-up of asymptomatic carriers remains essential to enable early detection and timely treatment.

GENETIC NEUROPATHIES

Abstract P098 - Cod. 143260

PHYSIOTHERAPY IN CHARCOT-MARIE-TOOTH DISEASE: WHAT THE ITALIAN CMT REGISTRY TELLS US

Cavalca E.^{*1}, Bertini A.¹, Serio M.¹, Manganelli F.², Fabrizi G.M.³, Schenone A.⁴, Santoro L.², Cavallaro T.³, Grandis M.⁴, Previtali S.⁵, Falzone Y.⁵, Allegri I.⁶, Padua L.⁷, Pazzaglia C.⁷, Saveri P.¹, Quattrone A.⁸, Valentino P.⁸, Vita G.⁹, Tozza S.², Gentile L.⁹, Russo M.⁹, Mazzeo A.⁹, Ferraro F.¹⁰, Pisciotta C.¹, Pareyson D.¹

¹ Unità di Malattie Neurologiche Rare, Dipartimento di Neuroscienze Cliniche, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ² Dipartimento di Neuroscienze, Scienze Riproduttive ed Odontostomatologiche, Università Federico II di Napoli, Napoli, Italy, ³ Dipartimento di Neuroscienze, Biomedicina e Movimento, Università di Verona, Verona, Italy, ⁴ Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze materno-infantili, Università di Genova, Genova, Italy, ⁵ INSPE e Divisione di Neuroscienze, IRCCS Ospedale San Raffaele, Milano, Italy, ⁶ Dipartimento di Neurologia, Azienda Ospedaliera di Parma, Parma, Italy, ⁷ Università Cattolica del Sacro Cuore, Rome, Italy, ⁸ Centro di Ricerche Neuroscienze e Istituto di Neurologia, Università Magna Graecia, Catanzaro, Italy, ⁹ Unità di Neurologia e Malattie Neuromuscolari, Dipartimento di Medicina Clinica e Sperimentale, Università di Messina, Messina, Italy, ¹⁰ Struttura Complessa di Riabilitazione Neuromotoria ASST Mantova Presidio di Bozzolo, Mantova, Italy

CMT treatment is still symptomatic. Despite extensive use of physiotherapy, no specific guidelines exist for adults. Data from direct patients' experience concerning access, benefits and satisfaction are lacking. We investigated physiotherapy use, satisfaction and access in a well-characterized CMT cohort.

Questionnaires were administered through the Italian CMT Registry (2015-2018) or at clinic of Besta Institute (2024), collecting also clinical and genetic data. Questionnaires: Foot Function Index-FFI; tailored Questionnaire developed with input from experts and patients' groups about physiotherapy use, benefit duration, satisfaction (VAS scale 0-10).

313 patients completed the questionnaire: 255 (81.5%) online and 58 (18.5%) in person. 210 (69.3%) received physiotherapy at least once. Compared to patients who never underwent physiotherapy, they showed higher CMTES (9.6 ± 5.1 vs 6.4 ± 4.5 ; $p < 0.001$); FFI pain ($20.8 \pm 17.9\%$ vs $13.9 \pm 15.2\%$; $p = 0.002$), FFI Disability scores ($34.7 \pm 17.5\%$ vs $22.1 \pm 18.2\%$; $p < 0.001$) and more frequent or-

thoses use (29.5% vs 5.8%; $p < 0.0001$). Most patients received physiotherapy in cycles (62.3%) through the National Health System (76.2%). Commonly reported interventions included stretching, muscle strengthening, posture and balance exercises, with 70% reporting at least three combinations. 62% of patients rated their satisfaction $\geq 6/10$. Perceived benefit lasted 1-3 months (57%), 3-6 months (17%) and more than 6 months in 12% of cases. 47% of patients reported difficulties accessing physiotherapy.

In conclusion, almost 70% of patients underwent physiotherapy at least once in their lives, with combined exercises and good satisfaction in most cases. However, duration of perceived benefit is limited, lasting less than 6 months for 75% of patients and access remains a significant barrier.

GENETIC NEUROPATHIES

Abstract P100 - Cod. 143415

QUANTITATIVE ASSESSMENT OF HAND MOTOR PERFORMANCE ACROSS DISEASE STAGES IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: RESULTS FROM THE MULTICENTER EULA PROJECT

Hamedani M.^{*1}, Prada V.², Massucco S.¹, Roveta E.¹, Grandis M.³, Gemelli C.², Schiavetti I.⁴, Signori A.⁴, Schenone C.¹, Luigetti M.⁵, Guglielmino V.⁶, Sciarrone M.A.⁶, Vitali F.⁶, Pradotto L.G.⁷, Manganelli F.⁸, Tozza S.⁸, Palumbo G.⁸, Mazzeo A.⁹, Gentile L.⁹, Russo M.⁹, De Luca M.⁹, D'Arma F.⁹, Pisciotta C.¹⁰, Fenu S.¹⁰, Pareyson D.¹⁰, Schenone A.³

¹ University of Genova, Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINO GMI), Genova, Italy, ² Italian Multiple Sclerosis Foundation, AISM, Genova, Italy, ³ Azienda Ospedaliera Metropolitana (AOM), Genova, Italy, ⁴ University of Genoa, Department of Health Sciences (DISSAL), Genova, Italy, ⁵ Fondazione Policlinico A. Gemelli IRCCS. UOC Neurologia, Rome, Italy, ⁶ Università Cattolica del Sacro Cuore. Dipartimento di Neuroscienze, Rome, Italy, ⁷ Ivrea Civil Hospital - ASLTO4, Ivrea, Italy, ⁸ Department of Neurosciences, Reproductive and Odontostomatology Sciences, University of Naples "Federico II", Naples, Italy, ⁹ University of Messina, Department of Clinical and Experimental Medicine, Messina, Italy, ¹⁰ Fondazione IRCCS Istituto Neurologico Carlo Besta. Department of Clinical Neuroscience, Milan, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a multisystem disease in which early neuropathy is often difficult to detect.

This study assessed hand motor performance using Hand Test System (HTS), comparing disease stages, controls, and clinical measures.

A total of 113 participants were evaluated at baseline (T0), 6 months (T1), and 1 year (T2): 74 ATTRv patients (FAP0:pre-symptomatic $n = 16$, FAP1:mild sensory/motor $n = 40$, FAP2:ambulatory with assistance $n = 18$) and 39 healthy controls. Assessments included 9-Hole Peg Test(9HPT), grip and pinch dynamometry, Thumb Opposition Test (TOT), Norfolk QoL, DASH, Neuropathy Impairment Score (NIS) scales, and HTS which measures touch-duration (TD), inter-tap interval (ITI), and movement rate(MR) during finger tasks.

HTS parameters did not show significant changes over time for right hand(RH) and left hand(LH). However, in the Finger Tapping task,

temporal parameters (TD and ITI) showed a slight increase, indicating worsening motor performance. In the complete sequence, MR decreased over time, also reflecting reduced motor performance. Standard clinical tests were stable over time. 9HPT showed comparable results over time (RH:p = 0.71; LH:p = 0.57). Grip strength and tripod pinch did not change significantly in either hand (grip RH:p = 0.73; LH:p = 0.70; pinch RH:p = 0.64; LH:p = 0.74). The TOT also remained stable. Subjective and clinical scales showed no significant changes in mean scores (DASH:p = 0.38; Norfolk QoL:p = 0.60; NIS:p = 0.98). A slight worsening at T2 was observed in FAP2 patients on the NIS scale, but no significant differences emerged among subgroups.

Instrumental and clinical measures remained stable across T0–T2, likely reflecting treatment effects. Although not statistically significant, HTS was more sensitive than standard assessments for subtle motor changes. Larger, longer studies are needed.

GENETIC NEUROPATHIES

Abstract P102 - Cod. 143066

RESPIRATORY UPDATES IN CANVAS

Zuccarino R.*, Stano S., Mercuriali B., Cesaretti E., Corradi E., Foschi L., Ferrari V., Mase Gallizzioli C.
Centro NeMO Trento, Trento, Italy

The phenotypic spectrum associated with biallelic RFC1 AAGGG repeat expansion includes Cerebellar Ataxia, with Neuropathy, and Vestibular Areflexia Syndrome (CANVAS).

Moreover a chronic spasmodic dry cough is frequently also associated. Despite patients often report sleep disturbance, no data are found in the literature regarding the incidence of sleep breathing disorders in subjects affected by CANVAS.

A respiratory evaluation protocol (CANVASleep) including the Epworth Sleepiness Scale (ESS), Fatigue Severity Scale (FSS), Force Vital Capacity (FVC), Polysomnography (PSG) was assessed to individuals diagnosed with CANVAS.

To date 10 CANVAS patients have been evaluated with the CANVASleep: 5 F, 5 M, mean age 60 (range 47–73). The mean score of the ESS was 7.2 (range 3–10), of the FSS was 32 (range 19–46). The mean value of the FVC was 3.6 liters (89%) and the PSG showed 11.85 as mean value of the Apnoea-Hypopnoea Index (AHI) (range 5.7–18), associated with Cheyne-Stokes breathing in 4 individuals and for that reason the CPAP was introduced. All patients complained cough. The study is still ongoing.

These are preliminary data from 10 patients and additional results will be included at the meeting. Results from this study will help to focus future studies to understand the impact of sleep-disordered breathing in CANVAS to better improve the management of individuals with CANVAS. Further, the results provide objective data that can be used in developing specific interventions which could improve the quality of life of patients.

GENETIC NEUROPATHIES

Abstract P104 - Cod. 143507

STABILIZATION OF MIXED PHENOTYPES IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS UNDER VUTRISIRAN THERAPY

Gianoli M.*¹, Fasano C.¹, Longhi S.², Ruotolo I.³, Roberto D.¹, Rinaldi R.¹, Provini F.¹, Calandra--Buonaura G.¹, Guaraldi P.¹

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, University of Bologna, Bologna, Italy., Bologna, Italy., ² Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy., Bologna, Italy., ³ University of Bologna, Department of Medical and Surgical Sciences (DIMEC), Bologna, Italy., Bologna, Italy

Hereditary transthyretin amyloidosis (ATTRv) is a systemic disorder caused by the deposition of misfolded transthyretin, characterized by heterogeneous multiorgan involvement, commonly affecting the peripheral nervous system and the heart. Disease-modifying therapies have changed the natural history of ATTRv; however, real-world data on patients carrying mutations associated with a mixed cardiac-neurological phenotype remain limited.

We analyzed a real-world cohort of ATTRv patients, focusing on individuals carrying the Ile68Leu mutation, typically associated with a mixed phenotype. Cardiac involvement was assessed using the New York Heart Association (NYHA) functional classification, while neuropathic burden was evaluated using the Familial Amyloid Polyneuropathy (FAP) scale. Neuropathy-related disability was assessed using the Norfolk Quality of Life–Diabetic Neuropathy (Norfolk QOL-DN) questionnaire. Longitudinal changes were evaluated over a follow-up period of up to 18 months.

Among 57 ATTRv patients, 29 (50%) carried the Ile68Leu mutation. At baseline, most patients were classified as NYHA class I (48%), a distribution that remained stable throughout follow-up. Neuropathic involvement was mild but present, with the majority of patients presenting with FAP stage 1 (83%), and remained stable over time. At 9 months, two patients experienced cardiovascular events, with complete resolution and stabilization at 18 months of follow-up. Baseline NYHA class did not independently influence disability at 9 months, as assessed by the Norfolk QOL-DN ($r = 0.13$, $p = 0.56$), indicating no association between initial cardiac burden and subsequent global neuropathic disability.

In ATTRv patients with a mixed cardiac-neurological phenotype, treatment with vutrisiran was associated with global stabilization of disease manifestations.

GENETIC NEUROPATHIES

Abstract P106 - Cod. 143430

STATIC AND DYNAMIC STABILOMETRIC EVALUATION AND REHABILITATION IN PERIPHERAL NEUROPATHY

Schenone C.*¹, Hamedani M.¹, Roveta E.¹, Massucco S.¹, Gemelli C.², Grandis M.², Barone C.¹, Leandri M.¹, Schenone A.²

¹ Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics,

Maternal and Child Health (DINOEMI), University of Genoa, Genoa, Italy,
² *Department of Neurology, IRCCS Azienda Ospedaliera Metropolitana
 Ospedale Policlinico San Martino, Genoa, Italy*

Charcot Marie Tooth (CMT) disease is a hereditary peripheral neuropathy with progressive distal muscle weakness, sensory impairment and balance dysfunction, leading to gait instability and increased fall risk.

This study aims to evaluate the reliability and responsiveness of a static and dynamic stabilometric platform (SP) in individuals with CMT.

Preliminary data are available from 24 patients and 30 HC. Eligibility criteria were age 18-80 years, absence of significant comorbidities, no recent orthopedic surgery, and a pain score < 3 on the Visual Analogue Scale. All participants underwent balance assessment using the SP under static conditions (eyes open, eyes closed) and dynamic conditions (eyes open toes-up perturbation, eyes open backward stimulation). During dynamic trials, surface electromyography assessed activation timing of the tibialis anterior and soleus muscles. Patients with CMT also performed the Berg Balance Scale, Modified Barthel Index, Tinetti Scale, 10-Meter Walk Test and 6-Minute Walk Test. Patients were randomized to traditional physiotherapy or platform-based rehabilitation, both consisting of 30 daily 1-hour sessions.

No significant test-retest differences were observed in HC, confirming platform reliability. In CMT patients, significant post-treatment improvements were found in Sway Area and Sway Path during static conditions ($p = 0.01$). Sway Area correlated with activation timing of the tibialis anterior ($r = 0.65$, $p = 0.03$) and soleus ($r = 0.72$, $p = 0.01$). Significant post-treatment improvements were also observed in clinical scales ($p < 0.05$).

Overall, the stabilometric platform proved reliable and sensitive in detecting balance deficits and rehabilitation-related changes in CMT patients, providing objective measures that complement traditional clinical assessments.

GENETIC NEUROPATHIES

Abstract P108 - Cod. 142774

TO BE OR NOT TO BE PRESYMPTOMATIC: DIAGNOSTIC VALUE OF CARPAL LIGAMENT AMYLOID DEPOSITION IN TRANSTHYRETIN AMYLOIDOSIS

Alfano F.*, Guglielmino V., Vitali F., Sciarrone M.A., Siconolfi G., Luigetti M.

Università Cattolica del Sacro Cuore, Roma, Italy

Hereditary transthyretin amyloidosis (ATTRv, v for variant) is a rare, progressive and heterogeneous disease with multisystemic involvement, caused by autosomal dominant mutations in TTR gene. If untreated, the condition is life-threatening. In the era of disease-modifying therapies, early diagnosis in mutation carriers is crucial to enable timely therapeutic intervention.

We describe a 49-year-old man carrying a heterozygous TTR mutation (p.Glu109Gln), identified through genetic testing in 2013, per-

formed because of a positive family history.

Since then, the patient has undergone regular extensive multidisciplinary follow-up, including cardiological and neurological clinical and instrumental evaluations.

At last follow-up, patient started to complain mild diarrhoea without weight loss. Clinical and instrumental evaluations, including skin biopsies, were unremarkable.

The patient underwent carpal tunnel release for paraesthesia of the left hand, and the ligamentous tissue was collected. Histopathological examination revealed amorphous fibrillar material with positive Congo Red staining and apple-green birefringence under polarized light, consistent with amyloid deposition.

In ATTRv carpal tunnel syndrome is not considered the onset of neuropathy. However, amyloid deposition in tissues suggests ongoing disease. Considering the symptoms compatible ATTRv reported by the patient, we wonder whether disease onset can be established in this case.

This report emphasizes the importance of pursuing the earliest possible diagnosis in ATTRv to improve patients' prognosis through timely therapy initiation.

GENETIC NEUROPATHIES

Abstract P110 - Cod. 143235

UNSTEADINESS IN CMT: DOES SUBTYPE MATTER?

Aiello A.*¹, Fiumarella R.¹, Castiglia M.¹, Dell'Aversana D.¹, Cassano E.², Canale F.³, Nolano M.¹, Manganelli F.¹, Tozza S.¹

¹ *Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples Federico II, Naples, Italy,* ² *Neurology Unit, Ospedale del mare, Naples, Italy,* ³ *Neurology Unit, University Hospital Federico II, Naples, Italy*

Charcot-Marie-Tooth (CMT) diseases are a clinically and genetically heterogeneous group of peripheral neuropathies. Among symptoms CMT patients can complain of balance disturbance.

The aim of this study was to define the imbalance in CMT population and in the most frequent subtype. We recruited 255 genetically confirmed CMT patients (duplication PMP22, MPZ, GJB1, MME) and retrospectively collected clinical data focusing on imbalance symptoms, weakness of anterior and posterior leg muscles, and overall disability computed by CMT Examination Score (CMTES).

Unsteadiness is present in the overall cohort in 27.1%. Patients with balance disturbance were older (57.9 ± 14 vs 40.1 ± 17.8 ; $p < 0.001$), had longer disease duration (27.8 ± 17.6 vs 14.2 ± 12.6 ; $p < 0.001$) and showed greater disability (CMTES 13.6 ± 3.9 vs 5.8 ± 3.9). Balance disturbance is associated with more frequent involvement of posterior muscle (59 vs 10; $p < 0.001$) involvement. Although not significant, unsteadiness was more frequent in CMT-MPZ 40.9% compared to other genotype (23.8% in CMT1A, 30.9% in CMTX, 36.3% of CMT2T) and occurred in younger age in CMTX (50.9 ± 13.2) respect the other subtype (CMT1A 58.3 ± 17.7 , CMT-MPZ 63.5 ± 10.9 , CMT2T 63.5 ± 13.7).

Postural unsteadiness can be a major problem in about one third of CMT patients, especially those with advanced age, longer disease

duration and greater clinical disability. Posterior leg muscle involvement was confirmed as the main responsible for balance disturbances. Moreover, the frequency and earlier onset of unsteadiness may vary among genetic subtypes, with GJB1 patients showing earlier manifestations. These findings highlight the importance of assessing balance in routine clinical evaluation of CMT and may inform subtype-specific management strategies.

GENETIC NEUROPATHIES

Abstract P112 - Cod. 143385

VUTRISIRAN IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS WITH POLYNEUROPATHY: AN ITALIAN NATIONWIDE REAL-LIFE STUDY

Tozza S.⁴, Sciarone M.A.¹, Guaraldi P.², My F.³, Aiello A.⁴, Baldini T.⁵, Barilaro A.⁶, Briani C.⁷, Brighina F.⁸, Burattini M.⁹, Cambieri C.¹⁰, Castiglia M.⁴, Ceccanti M.¹⁰, Currò Dossi M.¹¹, Di Marzio F.¹², Di Stefano V.⁸, Falzone Y.¹³, Fasano A.³, Fasano C.², Fenu S.¹⁴, Filosto M.¹⁵, Frigeni B.¹⁷, Forcina F.¹⁶, Gemelli C.¹⁸, Gentile L.¹⁹, Gianoli M.², Ginanneschi F.²⁰, Grandis M.²¹, Goglia M.²², Leonardi L.¹⁶, Lozza A.²³, Mazzeo A.¹⁹, Milani R.²⁴, Mollo U.⁶, Musinelli R.²³, Obici L.²³, Pareyson D.¹⁴, Piscosquito G.²⁵, Poli L.²⁶, Pradotto L.G.²⁷, Ratti A.¹³, Russo M.¹⁹, Salvalaggio A.⁷, Siconolfi G.¹, Sist C.²⁸, Spinelli S.¹⁷, Tagliapietra M.²⁹, Verriello L.³⁰, Vitali F.¹, Manganelli F.⁴, Luigetti M.¹

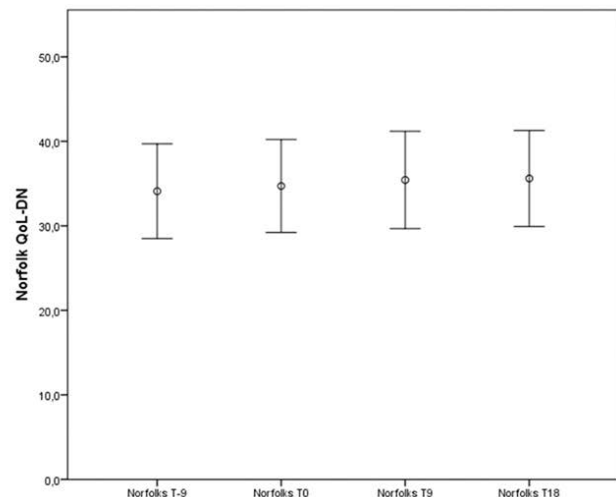
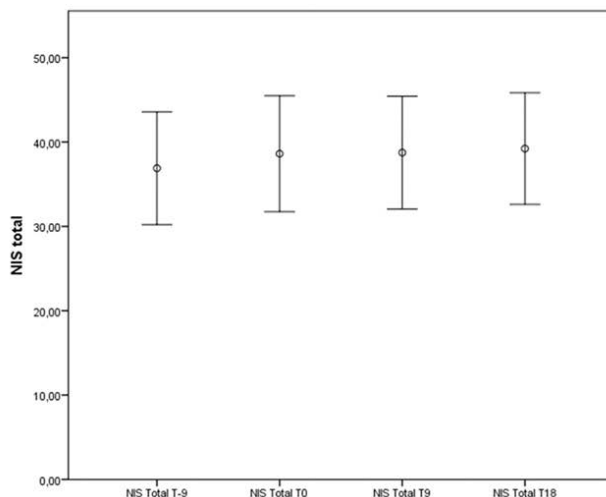
¹ Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ² IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ Division of Neurology, Ospedale V. Fazzi, Lecce, Italy, ⁴ Department of Neuroscience, Reproductive and Odonstomatological Science, University of Naples Federico II, Naples, Italy, ⁵ Ospedale Infermi Rimini, AUSL Romagna, Rimini, Italy, ⁶ AOU Careggi and Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy, ⁷ Neurology Unit, Department of Neuroscience, University of Padua, Padua, Italy, ⁸ Department of Biomedicine, Neuroscience and Advanced Diagnostics (BIND), University of Palermo, Palermo, Italy, ⁹ Neurology Unit, Ospedale Santa Croce di Fano, Fano, Italy, ¹⁰ Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy, ¹¹ Department of Neurology, Santa Maria delle Croci Hospital, Ravenna, Italy, ¹² Division of

Neurology, Madonna del Soccorso Hospital, San Benedetto del Tronto, Italy, ¹³ Department of Neurology, Institute of Experimental Neurology, San Raffaele Scientific Institute, Milan, Italy, ¹⁴ S.C. Malattie Neurologiche Rare, Dipartimento di Neuroscienze Cliniche, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ¹⁵ NeMO-Brescia Clinical Center for Neuromuscular Diseases: Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, ¹⁶ Neuromuscular and Rare Disease Centre, Neurology Unit, Sant'Andrea Hospital, "Sapienza" University of Rome, Rome, Italy, ¹⁷ USC Neurologia, ASST Papa Giovanni XXIII, Bergamo, Italy, ¹⁸ IRCCS Azienda Ospedaliera Metropolitana, Genoa, Italy, ¹⁹ Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy, ²⁰ Dipartimento di Scienze Mediche, Chirurgiche e Neuroscienze, Università di Siena, Siena, Italy, ²¹ IRCCS Ospedale Policlinico San Martino, Genoa, Italy, ²² Neuromuscular Diseases Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ²³ Amyloidosis Research and Treatment Centre, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy, ²⁴ Department of Neurosciences, Neurology and Stroke Unit, "Alessandro Manzoni" Hospital, Lecco, Italy, ²⁵ Neurology Unit, University Hospital "San Giovanni di Dio e Ruggi d'Aragona", University of Salerno, Salerno, Italy, ²⁶ Unit of Neurology, ASST Spedali Civili, Brescia, Italy, ²⁷ Department of Neuroscience, University of Turin, Turin, Italy, ²⁸ Dipartimento di Neurologia/Stroke Unit, Ospedale di Bolzano, Bolzano, Italy, ²⁹ Department of Neuroscience, Biomedicina e Movimento, Università di Verona, Verona, Italy, ³⁰ Neurology Unit, Department of Head-Neck and Neurosciences, University Hospital Santa Maria della Misericordia, Udine, Italy

This study aimed to evaluate the Italian real-life experience with vutrisiran in patients with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN).

We enrolled genetically confirmed ATTRv-PN patients treated with vutrisiran from 29 Italian amyloidosis referral centres. Consecutive clinical data were collected (T0, T9, T18), including familial amyloid polyneuropathy (FAP) stage, Neuropathy Impairment Score (NIS), Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QoL-DN) questionnaire and Compound Autonomic Dysfunction Test (CADT). Cardiological outcomes included New York Heart Association (NYHA) functional class and cardiovascular events.

A total of 374 ATTRv-PN patients were enrolled, of whom 263 (70.3%) were male. The mean age at disease onset was 64.4±11.6 years and the mean age at first treatment was 66.2±11.7 years. 29.7%



patients were drug-naïve, while the remained subjects switched from another therapy.

At baseline (T0), 28.3% of patients presented with a predominantly neurological phenotype, while 71.1% had a mixed phenotype. At the last available follow-up, 98.7% of patients remained stable in their clinical phenotype. FAP stage remained stable throughout follow-up, as well as neurological (NIS, Norfolk, CADT) and cardiological outcome.

Vutrisiran represents an effective therapeutic option for the management of patients with ATTRv amyloidosis, demonstrating stabilization of clinical phenotype as well as neurological and cardiological involvement in a real-world setting.

GENETIC NEUROPATHIES

Abstract P114 - Cod. 143339

ZFHX3-RELATED SPINOCEREBELLAR ATAXIA TYPE 4 EXPANSION CAUSES COMPLEX ATAXIA WITH NEUROPATHY AND CANVAS-LIKE SYNDROME

Pizzuto F.², Quartesan I.², Facchini S.², Bertini A.¹, Currò R.², Wood N.², Houlden H.², Cortese A.²

¹ Unit of Rare Neurological Diseases, Department of Clinical Neurosciences, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy,

² Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom

Spinocerebellar ataxia type 4 (SCA4) is a rare autosomal dominant neurodegenerative disorder characterized by progressive cerebellar ataxia, sensory neuropathy, dysautonomia and motor neuron involvement. In 2024, an exonic GGC-repeat expansion in ZFHX3 was identified as the cause of SCA4 in multiple families of Scandinavian ancestry. Here we report two related English individuals with progressive ataxia and neuropathy carrying pathogenic SCA4 expansion. Patients underwent clinical, neurophysiological and neuroimaging assessments. Genetic investigations included whole-exome sequencing (WES) and whole-genome sequencing (WGS) with panels for hereditary ataxia and neuropathy, repeat expansion testing and mitochondrial DNA sequencing. Targeted analysis on WGS was performed using ExpansionHunter.

The father presented in his 30s with progressive ataxia, upper limb-predominant sensorimotor neuropathy, dystonic tremor and dysautonomia. Brain MRI demonstrated cerebellar and medullar atrophy. His son developed predominantly sensory ataxia in his 40s, associated with cough and neuropathy/neuronopathy on nerve conduction studies, but normal brain MRI. WES performed in the father identified a heterozygous PRKCG variant of uncertain significance (c.1372G > A, p.Ala458Thr), however the phenotype was considered atypical for SCA14 and the variant did not segregate in the family. Also inflammatory, metabolic, paraneoplastic and genetic causes for complex ataxia, including RFC1 expansions, were excluded. Targeted analysis on WGS revealed a heterozygous 52 GGC-repeat expansions in ZFHX3 in both individuals.

This report highlights the importance of genomic reanalysis, particularly when phenotype does not fully align with identified genetic

variants. ZFHX3 testing should be considered in progressive ataxia with sensory neuropathy and CANVAS-like phenotype with sensory neuropathy and cough, even outside Scandinavian populations.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P116 - Cod. 143270

A PAINFUL LUMBOSACRAL RADICULOPLEXOPATHY IN A NON-DIABETIC PATIENT EXPOSED TO TIRZEPATIDE: EXPANDING THE SPECTRUM OF GLP-1RA-ASSOCIATED NEUROPATHIES

Stabile L.^{*1}, Poli L.², Bozzoni V.², Padovani A.², Filosto M.¹

¹ University of Brescia, Brescia, Italy, ² ASST Spedali Civili di Brescia, Brescia, Italy

Lumbosacral radiculoplexopathy (LRP) classically occurs in patients with diabetes mellitus. Emerging evidence suggests a possible association between glucagon-like peptide-1 receptor agonists (GLP-1RAs) and LRP; however, data in non-diabetic individuals remain limited. We report a case of LRP in a non-diabetic patient exposed to tirzepatide, suggesting potential immuno-metabolic triggers beyond diabetes.

A 62-year-old man treated with tirzepatide for weight loss developed acute left-sided low back pain followed by severe neuropathic pain, distal weakness, and sensory deficits. Neuroimaging demonstrated involvement of the left L5 nerve root and sciatic nerve with denervation edema. Cerebrospinal fluid analysis showed marked hyperproteinorrachia without pleiocytosis. Electrophysiological studies confirmed left lumbosacral plexopathy. Glycaemic parameters remained within the non-diabetic range throughout the disease course. Extensive investigations excluded infectious, neoplastic, paraneoplastic, and systemic inflammatory causes. Treatment with high-dose intravenous methylprednisolone followed by oral prednisone taper, combined with neuropathic pain therapy, resulted in complete pain resolution. Motor recovery was partial, with persistent weakness of left ankle dorsiflexion, consistent with residual axonal injury.

Tirzepatide exposure was associated with a rapid metabolic shift, including significant weight loss (5.6% over two months) and a reduction in HbA1c despite baseline normoglycaemia. The magnitude and rapidity of these changes suggest an acute catabolic state potentially impairing endoneurial metabolic homeostasis and microvascular regulation. Rapid metabolic modulation, rather than absolute glycaemic values, may increase susceptibility to focal ischaemic-inflammatory nerve injury.

This case supports the hypothesis that GLP-1RA-induced metabolic changes may act as a trigger or permissive factor for LRP independent of overt diabetes mellitus.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P118 - Cod. 143470

AN UNUSUAL PRESENTATION OF GUILLAIN-

BARRE' SYNDROME IN AN INFANT WITH PRIMARY, RAPIDLY DESCENDING PROGRESSIVE AXIAL MUSCLE INVOLVEMENT: A CASE REPORT

Dimatteo K.^{*1}, Di Pisa V.², Fetta A.¹, Capoferri E.², Casanova M.², Cordelli D.M.¹

¹ Department Of Medical And Surgical Sciences (dimec), Bologna, Italy, ² IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Neuropsichiatria dell'Età Pediatrica, Bologna, Italy

Guillain-Barré syndrome (GBS) is an immune-mediated acute polyradiculoneuropathy characterized by rapidly progressive weakness and areflexia, with significant morbidity.

We describe an atypical pediatric case of GBS with initial descending axial muscle involvement and subsequent progression to limbs and respiratory failure.

An 11-month-old previously healthy boy was hospitalised for neck weakness, reduced responsiveness, and bilateral acute otitis media. Neurological status rapidly deteriorated, with loss of independent sitting, ineffective cough, and poor sucking, requiring mechanical ventilation and enteral feeding. Dysautonomia developed with arterial hypertension. Spinal MRI showed contrast enhancement of nerve roots and cauda equina. Cerebrospinal fluid analysis revealed elevated protein levels, pleocytosis, and blood-brain barrier disruption. Autoimmune testing was negative. Electroneurography (ENG) demonstrated a predominantly axonal motor polyneuropathy. The patient was treated with intravenous immunoglobulin (IVIg, 2 g/kg over two days), resulting in progressive improvement, extubation, and return to oral feeding within 7–10 days. No triggering etiology was identified, and a diagnosis of likely post-infectious GBS was made. Follow-up ENG one month later showed predominantly demyelinating motor polyneuropathy despite clinical recovery. At 19 months of age, the child achieved complete neurological and functional recovery.

This case highlights an atypical presentation of GBS in infancy with primary axial muscle involvement. GBS should be considered in infants and toddlers even when the clinical course deviates from the classic ascending pattern.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P120 - Cod. 143223

ANTI-HMGCR IMMUNE-MEDIATED NECROTIZING MYOPATHY: CHARACTERIZATION OF A MONOCENTER COHORT AND DEVELOPMENT OF A THERAPEUTIC ALGORITHM

Molitierno N.^{*3}, Gagliardi D.³, Parisi M.³, Lerario A.², Ciscato P.², Bertolasi L.², Zanolini S.², Napoli L.², Ripolone M.², Cinnante C.M.⁴, Corti S.⁵, Comi G.P.¹, Velardo D.²

¹ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy, ² IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular and Rare Disease Unit, Milano, Italy, ³ IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy, ⁴ IRCCS Istituto Auxologico Italiano, Section of Neuroradiology, Department of Radiology and Diagnostic Imaging,

Milano, Italy, ⁵ Dino Ferrari Center, Department of Pathophysiology and Transplantation, Milano, Italy

Anti-HMGCR immune-mediated necrotizing myopathy is a rare autoimmune disease characterized by severe proximal muscle weakness, markedly elevated creatine kinase levels, and specific autoantibodies. Despite consensus recommendations, the lack of standardized criteria for therapeutic stratification represents a significant clinical challenge, particularly given the increasing recognition of phenotypic heterogeneity ranging from aggressive acute forms to chronic presentations.

This study aimed to characterize a monocenter cohort and develop objective criteria for therapeutic decision-making and prognostic stratification in anti-HMGCR myopathy.

We retrospectively analyzed 24 patients diagnosed between 2014–2025. Through multivariate analysis, we developed a therapeutic algorithm integrating baseline CK levels, MMT-8 scores, and MRI edema scores (AUC = 0.889), achieving 79.2% accuracy in predicting the need for multiple induction therapy. This approach produced comparable outcomes at 12 months between treatment groups (complete response: 50% vs 60%, $p = 0.697$). Prognostic analysis identified three significant baseline predictors of complete response: older age at onset, diagnostic delay, and degree of fibro-adipose replacement on MRI (AUC = 0.909). During follow-up, persistent muscle edema on MRI and need for rescue immunoglobulin therapy predicted suboptimal response (AUC = 0.898). Antibody kinetics analysis revealed correlations between antibody titre reduction and clinical response.

This study supports a multiparametric approach for personalized management of anti-HMGCR myopathy. The developed therapeutic algorithm enables objective stratification, while identification of prognostic factors facilitates early recognition of non-responders, improving patient outcomes.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P122 - Cod. 143525

ANTI-HU-ASSOCIATED SUBACUTE SENSORY NEURONOPATHY WITH NEUROBLASTOMA: A 35-YEAR PROTRACTED COURSE

Pauro A.^{*1}, Tierro B.¹, Cerantola E.¹, Sogus E.¹, Petrosino A.¹, Capece G.¹, Fornasier T.¹, Salvalaggio A.¹, Briani C.¹, Minicuci G.M.²

¹ Department of Neurosciences, University of Padova, Padova, Italy,

² Clinica Neurologica, Padova University Hospital, Padova, Italy

Anti-Hu antibody-associated subacute sensory neuronopathy (SSN) is the most frequent paraneoplastic neurological syndrome and is typically characterized by rapidly progressive sensory ataxia, although a protracted course may occur. Electromyography (EMG) usually demonstrates severe pure sensory involvement. In rare cases, SSN may be complicated by chronic intestinal pseudo-obstruction due to enteric neuropathy. Neuroblastoma is associated with several paraneoplastic syndromes, with anti-Hu antibodies representing the most common immunological marker.

We report a case of anti-Hu-associated SSN related to neuroblastoma with an exceptionally long clinical course.

In 1988, a 17-year-old woman was diagnosed with neuroblastoma of the left nasal cavity, not surgically resected, and treated with cisplatin and vincristine. Chemotherapy was discontinued after a few months because of the onset of foot paresthesias and gait impairment; EMG revealed a sensory neuropathy. She subsequently underwent radiotherapy, achieving radiological tumor remission. Several years later, particularly after childbirth in 1999, the patient experienced progression of lower-limb paresthesias and worsening ataxic gait. In 2010, she required surgery for chronic intestinal pseudo-obstruction with temporary stoma placement, later reversed. Subsequent EMG studies showed severe pure sensory neuronopathy. Based on the clinical and neurophysiological findings, a paraneoplastic etiology was suspected, and in 2014 anti-Hu antibodies were found to be strongly positive on serum Western blot and direct immunofluorescence. Whole-body PET-CT was negative, except for uptake in the left nasal fossa muscles, interpreted as muscle activation; multiple biopsies were negative. Repeated courses of intravenous immunoglobulins and plasmapheresis failed to provide clinical benefit, and the patient continues physical therapy.

This case illustrates that anti-Hu-associated SSN may follow an extremely slow clinical course, extending over more than 35 years, while remaining poorly responsive to immunomodulatory therapy.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P124 - Cod. 143467

ANTI-TR/DNER ANTIBODY-ASSOCIATED PERIPHERAL NEUROPATHY WITHOUT MALIGNANCY: A CASE REPORT

Vizziello M.^{*1}, Giordano A.¹, Cazzato D.², Izzo M.G.A.², Andreetta F.³, Riva N.¹, Usai S.¹, Lauria Pinter G.⁴, Dalla Bella E.¹

¹ Unit of Neurology 3 - Neuroalgology and Motor Neuron Disease Centre, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ² Milan, Italy, ² Neurophysiology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy, ³ Milan, Italy, ³ Unit of Neurology 4 - Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, ⁴ Milan, Italy, ⁴ Scientific Directorate, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy, Milan, Italy

Anti-Tr/DNER antibodies are classically associated with paraneoplastic cerebellar degeneration, most frequently related to Hodgkin lymphoma. Extracerebellar manifestations, including peripheral neuropathy, have rarely been described.

To report an atypical anti-Tr/DNER-associated peripheral neuropathy without malignancy.

We report a 53-year-old woman who developed progressive lower-limb pain starting in December 2021, followed by distal numbness and progressive gait impairment with falls. She also reported episodic muscle stiffness with delayed relaxation involving the hands and jaw. Neurological examination revealed distal lower-limb hypotrophy and weakness with bilateral foot drop, lower-limb areflexia,

stocking-distribution dysesthesias, and positive Romberg sign. Neurophysiological studies demonstrated an asymmetric, predominantly lower-limb sensorimotor neuropathy with mainly axonal features, minor demyelinating components, chronic neurogenic changes, mild distal active denervation, and evidence of neuromuscular hyperexcitability at needle EMG. The hyperventilation-ischemia test was positive for spasmodophilia. Cerebrospinal fluid analysis was unremarkable. Extensive serum testing for acquired neuropathies identified anti-Tr/DNER antibodies. The patient had a history of HIV infection with undetectable viral load. Comprehensive oncological screening, including serum tumor markers and whole-body FDG-PET, excluded occult malignancies. Initial treatment with corticosteroids showed no clinical benefit and led to worsening of cramps and contractures. Intravenous immunoglobulin (IVIg) therapy was initiated, resulting in recovery of functional independence, and is currently ongoing in cyclic administration.

This case expands the clinical spectrum associated with anti-Tr/DNER antibodies, suggesting that peripheral neuropathy may represent an atypical immune-mediated manifestation even in the absence of malignancy. Recognition of this association is clinically relevant, as it should prompt comprehensive paraneoplastic screening and timely initiation of immunotherapy.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P126 - Cod. 143254

BURDEN OF ILLNESS AND UNMET NEEDS AMONG PATIENTS WITH CIDP: RESULTS FROM A REAL-WORLD SURVEY

Bonetto C.^{*1}, Paci S.¹, Arvin--Berod C.¹, Wright J.², Taylor Y.², Ringland C.², Sahar R.²

¹ argenx, Ghent, Belgium, ² Adelphi Real World, Bollington, United Kingdom

CIDP is a chronic immune-mediated neuropathy associated with long-term disability, fluctuating disease course, and substantial treatment burden. Although disease-modifying therapies are available, many patients continue to experience persistent neurological symptoms that impair daily functioning, mental health, and social participation. A comprehensive understanding of the clinical, functional, and societal burden of CIDP using real-world data is essential to identify unmet needs and support more patient-centered disease management

A secondary analysis was conducted using data from Adelphi's CIDP Disease Specific Programme™, a multinational, cross-sectional, real-world survey of neurologists and their consulting patients in France, Germany, Italy, Spain, and the United Kingdom. Neurologists completed clinical record forms for 542 patients, and a subset of 199 patients completed self-reported outcome measures assessing symptom severity, health-related quality of life, employment status, caregiver support, and treatment satisfaction

Despite treatment, more than half of patients reported moderate-to-severe symptoms, including sensory disturbances, muscle weakness, fatigue, and gait impairment. Nearly half required mobility aids, and 27% relied on caregiver support, frequently leading to changes in caregivers' employment status. Forty-two percent of patients were

not employed full-time, with CIDP cited as the main reason in over half of cases. Mean EQ-5D-5L utility values were substantially lower than general population norms, and anxiety and depression were more prevalent among patients with greater disease severity. CIDP is associated with a substantial and persistent burden despite ongoing treatment. The high impact on quality of life, functional independence, and work productivity highlights important unmet needs and emphasizes the need for optimized long-term management strategies.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P128 - Cod. 143520

CIDP FOLLOWED BY MOGAD: ANTI-MOG ASSOCIATED COMBINED CENTRAL AND PERIPHERAL DEMYELINATION

Eros C.^{*1}, Marco P.¹, Mariotto S.², Cerfeda S.¹, Tiero B.¹, Salvalaggio A.¹, Minicuci G.M.¹, Briani C.¹

¹ Neurology Unit, Department of Neuroscience, University of Padova, Padua, Italy, ² Neurology Unit, Department of Neurosciences, Biomedicine, and Movement Sciences, Verona, Italy

Combined central and peripheral demyelination (CCPD) represents a rare immunopathological entity with simultaneous or temporally separated involvement of both nervous systems. The pathogenesis remains incompletely understood, with heterogeneous presentations and unpredictable therapeutic responses. The role of anti-MOG antibodies in CCPD is particularly controversial, as MOG is predominantly CNS-expressed, yet peripheral demyelination has been reported in seropositive patients.

A 63-year-old man with four-year CIDP history (currently in stable disease) presented with acute neurological deterioration: progressive gait impairment, distal paresthesias and urinary retention. Comprehensive evaluation included neurological examination, nerve conduction studies, contrast-enhanced MRI, visual evoked potentials (VEP), extensive serological testing including anti-aquaporin-4 and anti-MOG antibodies, and cerebrospinal fluid (CSF) analysis.

Examination revealed asymmetric distal weakness, areflexia, impaired proprioception, and suspended sensory level (T5-right, T8-left). Electrophysiology confirmed severe sensory-motor demyelinating polyradiculopathy fulfilling EFNS/PNS CIDP criteria. MRI demonstrated extensive contrast-enhancing lesions with diffusion restriction involving cerebral hemispheres, corpus callosum, hypothalamus, brainstem, optic chiasm, cervical cord (C1-C4), and conus-epiconus (D11-L1) with cord swelling. VEP showed bilateral P100 latency prolongation. CSF revealed elevated protein (0.92g/L), mild pleocytosis (8cells/ μ L), and positive oligoclonal bands. Anti-aquaporin-4 antibodies were negative; anti-MOG antibodies were positive in CSF and serum (MOG-associated disease was diagnosed). High-dose methylprednisolone (5g total) produced minimal benefit. Plasma exchange (five sessions) achieved partial motor-sensory improvement with mild radiological regression.

This case underscores the diagnostic complexity of inflammatory disorders bridging peripheral and central nervous systems, defying conventional CIDP, multiple sclerosis, or MOG-associated-disease

phenotypes. Prompt recognition and early, intensive immunomodulatory therapy are crucial for such non-classical presentations.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P130 - Cod. 143041

CLINICAL COURSE AND TREATMENT RESPONSE IN MULTIFOCAL CIDP: A MULTICENTER RETROSPECTIVE ANALYSIS FROM THE ITALIAN CIDP REGISTRY

Laurini C.^{*3}, Gallo C.², Ratti A.³, De Lorenzo A.², Moret F.⁴, Ricciardi D.⁵, Carpo M.⁶, Inghilleri M.⁴, Vitali F.⁷, Luigetti M.⁷, Habetswallner F.⁵, Previtali S.C.¹, Nobile--Orazio E.², Doneddu P.², Falzone Y.M.¹

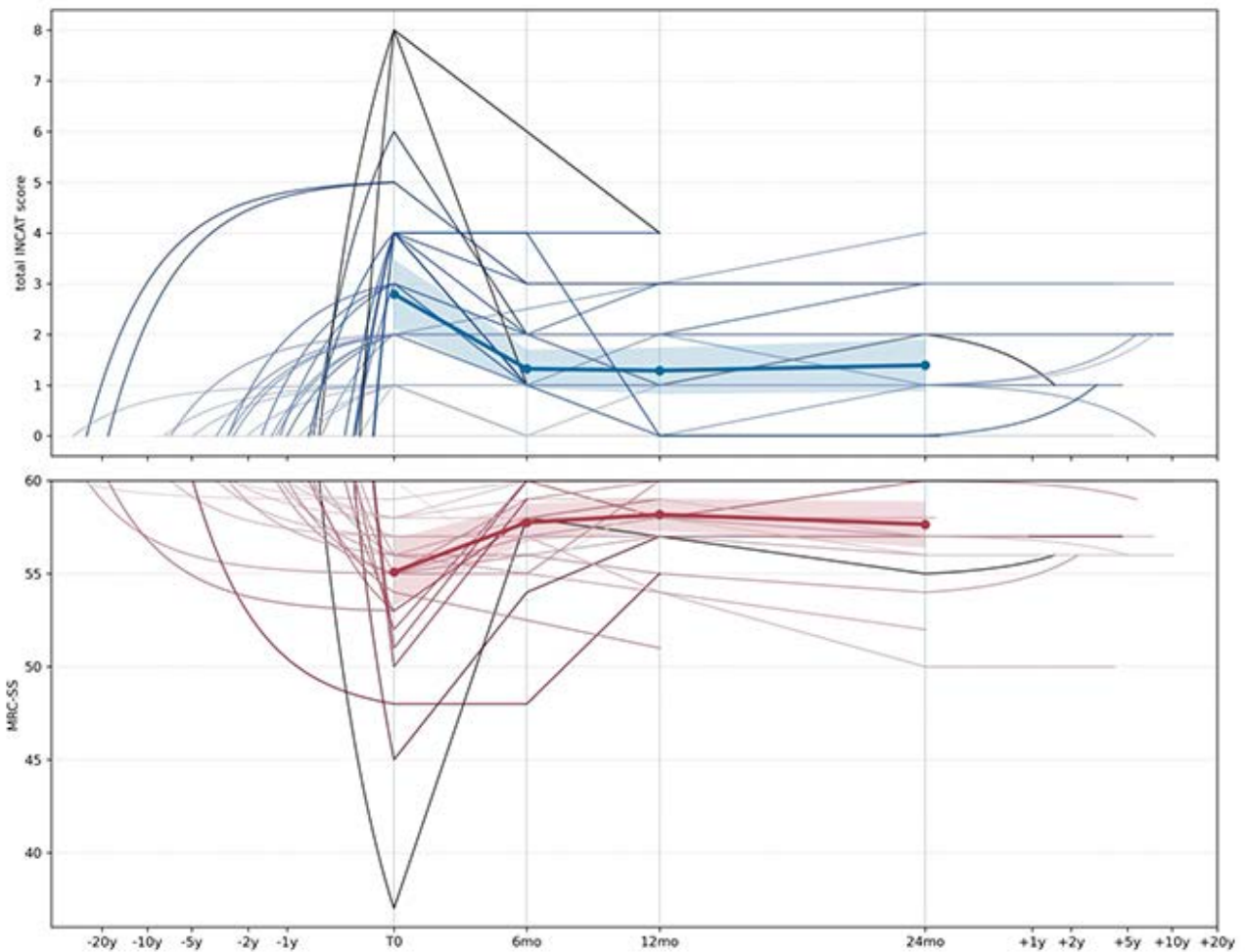
¹ Dipartimento di Neurologia, IRCCS Ospedale San Raffaele, Milano, Italy, ² Servizio Autonomo di Malattie Neuromuscolari e Neuroimmunologia, IRCCS Humanitas Clinical and Research Center, Milano, Italy, ³ Dipartimento di Neurologia, IRCCS Ospedale San Raffaele, Milano, Italy, ⁴ Dipartimento di Neuroscienze Umane, Università di Roma "Sapienza", Centro Malattie Rare Neuromuscolari, Policlinico Umberto I, Roma, Italy, ⁵ AORN Cardarelli Napoli, Unità di Neurofisiopatologia, Napoli, Italy, ⁶ UOC Neurologia, Azienda Ospedaliera Ospedale Treviglio Caravaggio, Treviglio, Italy, ⁷ Fondazione Policlinico Universitario A. Gemelli. UOC Neurologia, Roma, Italy

Multifocal CIDP is an uncommon CIDP phenotype with limited systematic descriptions in the literature. It remains unclear whether it represents an early phase of typical CIDP or a related but distinct entity, and whether its treatment-response profile mirrors that of typical CIDP.

We retrospectively identified patients with a diagnosis of multifocal CIDP from the Italian CIDP Registry and participating centers. Using a standardized case-report form, we collected demographics, baseline clinical phenotype, nerve involvement at onset, disability at T0 and at 6, 12, and 24 months, and treatment lines.

To date, 35 patients from seven centers have been included. Mean baseline age and INCAT were 53.2 years and 2.8 (95% C.I. = 2.1 - 3.5), respectively. At onset, the median, ulnar, and peroneal nerves were most frequently involved (69%, 66%, and 59%, respectively). Cranial nerve involvement occurred in 39% of patients, including bulbar symptoms, diplopia, facial palsy, and facial paresthesia, and almost invariably responded to treatment. Mean INCAT score and MRC-SS improved rapidly after treatment initiation (Fig. 1). Clinical response occurred in 84% of IVIg-treated patients. Among corticosteroid-treated patients, 59% improved, whereas 41% deteriorated and required escalation to alternative therapies. Overall, 4/35 patients were refractory to multiple lines of treatment, while 9/35 managed to discontinue all therapies due to clinical remission. Progression to a typical CIDP phenotype was observed in only one patient.

This study provides structured real-world data on multifocal CIDP phenotype, evolution, and treatment response. Additional enrollment is ongoing to achieve a sufficiently powered cohort for robust comparative analyses.



INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P132 - Cod. 143432

CLINICOPATHOLOGICAL FINDINGS IN POEMS SYNDROME: A CASE REPORT

Gentile F.¹, Laurini C.², Sorrenti B.², Russo T.², Schito P.², Quattrini A.¹, Filippi M.², Previtali S.², Falzone Y.M.²

¹ Unit of Experimental Neurology, Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy, ² Division of Neuroscience, IRCCS Ospedale San Raffaele, Milano, Italy

POEMS syndrome is a rare paraneoplastic neurologic disorder characterized by a monoclonal plasma cell disorder and a demyelinating neuropathy.

Distinction between POEMS syndrome and CIDP is critical due to different therapeutic approaches.

a 67-yo man presented to our attention with a 4-month history of rapidly progressive sensorimotor symptoms starting in the feet and ascending to the whole lower limbs and distal upper limbs. The pa-

tient was unable to walk independently, requiring double support, and on examination we observed leg and distal arm weakness, sensory ataxia, hypesthesia in the lower limbs and areflexia. Past medical history was notable for work-up on a recently discovered rib mass lesion suspicious for malignancy. Neuropathy work-up showed a sensorimotor demyelinating and axonal neuropathy in the four limbs on neurophysiology, albumino-cytological dissociation on CSF analysis and a double IgG λ /IgG κ monoclonal component on blood tests. A first trial of IVlg was ineffective and rather followed by clinical progression. Therefore, a nerve biopsy was performed, showing signs of active and chronic axonal changes together with signs of marked vasculopathy, such as neoangiogenesis, endothelial activation, hypertrophy and hyperplasia, raising suspicion for POEMS syndrome. Serum VEGF was then tested, demonstrating very high levels (4720 pg/mL). A biopsy of the bone lesion revealed solitary plasmacytoma, confirming the diagnosis.

herein we describe the clinic-pathological findings of a patient with POEMS syndrome. A marked vasculopathy on nerve sections should raise the suspicion of the disease and expedite serum VEGF testing to confirm the diagnosis.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P134 - Cod. 143258****CORRESPONDENCE BETWEEN PATIENTS' AND NEUROLOGISTS' SATISFACTION WITH TREATMENT IN PATIENTS WITH CIDP: RESULTS FROM A REAL-WORLD INTERNATIONAL SURVEY**

Bonetto C.^{*1}, Brackx F.², Arvin--Berod C.¹, Paci S.¹, Van De Veire L.², Taylor Y.³, Wright J.³, Dewilde S.²

¹ argenx, Ghent, Belgium, ² Services in Health Economics, Brussels, Belgium, ³ Adelphi Real World, Bollington, United Kingdom

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare, immune-mediated neurological disorder characterized by progressive or relapsing muscle weakness and sensory deficits, often requiring long-term immunomodulatory treatment. In CIDP, treatment success is influenced not only by clinical response but also by patient-perceived outcomes, including symptom control and treatment burden. Misalignment between patient and physician perceptions of treatment effectiveness may affect shared decision-making, treatment adherence, and disease management. This study assessed the level of agreement between treatment satisfaction reported by patients with CIDP and their treating neurologists in routine clinical practice.

Matched patient–physician data were analyzed from Adelphi's CIDP Disease Specific Programme™, a multinational, real-world, cross-sectional survey conducted between April 2022 and April 2023. Neurologists provided clinical data, while patients completed post-consultation questionnaires. Treatment satisfaction was rated by patients and neurologists as satisfied, neutral, or dissatisfied. Agreement was assessed using Cohen's weighted kappa statistic, with descriptive analyses used to explore discordance.

Among 199 matched patient–physician pairs, 82.4% receiving active treatment were included. 72% of patients reported being satisfied with treatment, 22% were neutral, and 7% were dissatisfied. Neurologists reported higher satisfaction, with 83% satisfied, 12% neutral, and 5% dissatisfied. Agreement was moderate, with concordant ratings in 82.2% of cases. When discrepancies occurred, neurologists more often rated satisfaction higher than patients, particularly when patients reported neutral satisfaction or dissatisfaction. Treatment satisfaction in CIDP was generally aligned between patients and neurologists; however, meaningful discrepancies remain. Greater integration of patient-reported outcomes into routine care may help reduce perception gaps and support more patient-centered treatment decisions.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P136 - Cod. 142785****EARLY PHYSIOTHERAPY INTERVENTION AFTER PARALYSIS DUE TO HERPES ZOOSTER INFECTION: A CASE REPORT**

Albino C.^{*1}, Condello C.¹, Furfari P.¹, Polistena G.¹, Vilasi A.D.², Torino C.², Mezzatesta S.²

¹ Recovery and Rehabilitation Unit, GOM "Bianchi-Melacrino-Morelli", Reggio Calabria, Reggio di Calabria, Italy, ² Institute of Clinical Physiology, National Research Council, Reggio Calabria, Italy

This paper reports the results of early rehabilitation management after hospitalization following post-infectious brachial palsy due to Herpes Zoster in a 72-year-old man. The intensive physiotherapy protocol included: passive and assisted active mobilization of the upper limb, segmental and integrated muscle strengthening, proprioceptive stimulation of the upper limbs, virtual reality exercises, and resistance training. Assessments included dynamic surface electromyography, the Medical Research Council scale for muscle strength and passive measurement of joint Range Of Motion, performed at baseline and 4, 10, 17 e 23 weeks to evaluate the effectiveness of physiotherapy treatment. This clinical case highlights the importance of timely diagnosis and integrated management in patients with post-herpetic neuropathies. In particular, early rehabilitative intervention may ensure a faster restoration of function and a return to normal daily activities.

Early rehabilitation intervention after hospitalization promotes a more rapid complete functional recovery of full muscle and articular function at 23 weeks. As shown in this case, an initial differential diagnosis is essential to rule out other pathologies [9]. Once a diagnosis is confirmed, a multidisciplinary approach is critical [6]. Recovery from SZP is generally expected within 1 to 2 years and has a favourable prognosis with complete or partial retrieval rate in 75% of cases [4]. Alongside medical treatment, early rehabilitation helps prevent muscle atrophy, joint stiffness, and manage pain [6; 10]. This case demonstrates that early rehabilitation after HZ infection can reduce complications and lead to timely functional recovery. Therefore, a multidisciplinary approach, which allows for early diagnosis and equally early rehabilitation, reduces the risk of complications, allowing for a better and more rapid restoration of joint mobility and strength.

Legend to table

Table 1. Evolution of Joint Range of Motion (ROM) (interval 0–X°).

Movement	T0 (25.05.2024)	T1 (20.06.2024)	T2 (19.08.2024)	T3 (20.09.2024)	T4 (30.10.2024)
Flexion (0–180°)	0–120°	0–130°	0–160°	0–180°	0–180°
Abduction (0–180°)	0–110°	0–130°	0–150°	0–180°	0–180°
Adduction (0–75°)	0–75°	0–75°	0–75°	0–75°	0–75°
External Rotation (0–90°)	0–50°	0–70°	0–90°	0–90°	0–90°
Internal Rotation (0–70°)	0–10°	0–60°	0–70°	0–70°	0–70°

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P138 - Cod. 143461

EFGARTIGIMOD SC IN PATIENTS WITH SEVERE RELAPSE OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP): A CASE REPORT

Dell'Aquila C.^{*}, Di Muzio M., De Liso A., Rinaldi G.
SC Neurologia Stroke Unit P.O. Di Venere, Bari, Italy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated neuropathy characterized by progressive or relapsing muscle weakness and sensory impairment, leading to functional disability and reduced quality of life¹. Recommended treatment for CIDP include high-dose IVIg, subcutaneous Ig, corticosteroids, and plasma exchange (PLEX). Other immunosuppressive agents are commonly used as add-on or treatment-sparing medication although supported by limited evidence of efficacy.

However, some patients may still experience ongoing disease activity with treatment dependence or high treatment burden.²

Efgartigimod, a human immunoglobulin (Ig)G1 antibody Fc fragment that reduces IgG recycling by blocking FcRn3, was demonstrated to be efficacious and safe in patients with CIDP4. In Italy, a Pre-Approval Access (PAA) program is ongoing to provide efgartigimod PH20 sc to CIDP patients with unmet medical needs who are ineligible for participation in clinical studies.

Case Report: We report an 82-year-old CIDP patient previously treated with monthly IVIg who required hospitalization due to a severe disease relapse (INCAT score 9) resistant to high-dose IVIg. Following transition to PLEX, the patient achieved partial clinical improvement but remained dependent on frequent exchanges after hospital discharge. The patient was subsequently enrolled in the PAA program and initiated once-weekly efgartigimod PH20 SC PFS with further

clinical improvement and recovery of functional independence (IN-CAT score 1) reporting no adverse events

This case illustrates the potential of efgartigimod as an effective and well-tolerated option for patients with CIDP who are refractory to or dependent on conventional therapies, and highlights its potential to reduce treatment burden while restoring patient autonomy.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P140 - Cod. 143274

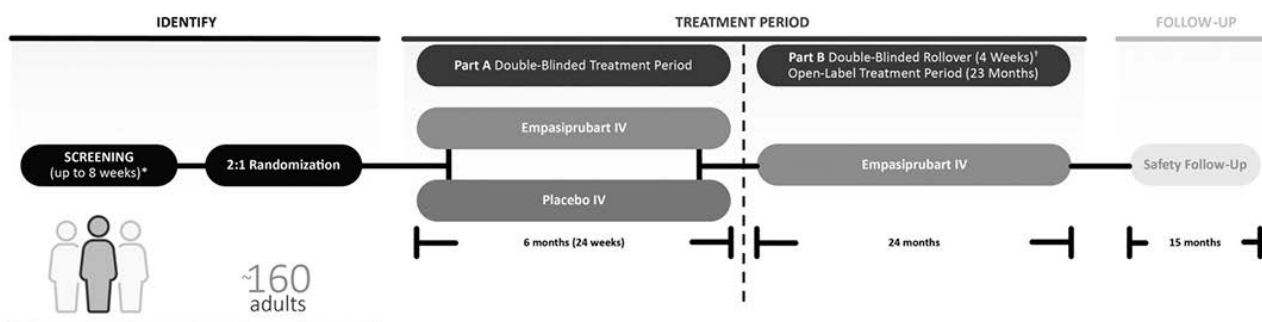
EMPASIPRUBART VERSUS PLACEBO IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: EMNERGIZE PHASE 3 STUDY DESIGN

Doneddu P.E.^{*8}, Rinaldi S.¹, Brannagan T.H.², Gable K.L.³, Stettner M.⁴, Querol L.⁵, Patel R.⁶, Haddad H.⁶, Van De Steen O.⁶, Budding K.⁶, Van De Walle I.⁶, Ellor S.⁶, Markov M.⁶, Allen J.A.⁷

¹ University of Oxford, Oxford, United Kingdom, ² Vagelos College of Physicians & Surgeons, Columbia University Irving Medical Center, New York, United States of America, ³ Duke University Medical Center, Durham, United States of America, ⁴ University Medicine Essen, Essen, Germany, ⁵ Hospital de La Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, ⁶ argenx, Ghent, Belgium, ⁷ University of Minnesota, Minneapolis, United States of America, ⁸ Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, 20089 Rozzano and Humanitas University, 20072 Pieve Emanuele, Milan, Italy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, autoimmune neuropathy characterized by nerve damage, resulting in disability due to limb weakness, sensory disturbances, and fatigue. Nerve biopsies in CIDP feature complement deposition. Additionally, complement activation promotes macrophage-mediated demyelination. Empasiprubarb binds complement C2, blocking acti-

Figure. EMNERGIZE Study Design



CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EAN, European Academy of Neurology; IV, intravenous; PNS, Peripheral Nerve Society.

*A diagnostic adjudication committee confirmed participant diagnosis. ¹Participants from the empasiprubarb arm will receive placebo once to maintain the blind of Part A. Empasiprubarb will be given as loading doses on Days 1 and 8, followed by maintenance doses every 4 weeks.

Key inclusion criteria: Meets criteria for CIDP based on EAN/PNS Task Force CIDP guidelines, second revision; has either typical CIDP or 1 of the following CIDP variants: motor CIDP (including motor-predominant CIDP), multifocal CIDP (also known as Lewis-Sumner syndrome), focal CIDP, or distal CIDP; has residual disability and active disease; has not received previous treatment for CIDP, or has stopped receiving CIDP treatment, or is receiving CIDP treatment (pulsed or oral corticosteroids, immunoglobulins, plasma exchange, or neonatal Fc receptor inhibitors).

Key exclusion criteria: Meets the criteria for possible CIDP based on EAN/PNS Task Force CIDP guidelines, second revision; sensory CIDP; other autoimmune diseases that may affect CIDP symptom assessments; polyneuropathy of other causes; clinical diagnosis of systemic lupus erythematosus; prior long-acting immunosuppressive/immunomodulatory treatment; prior treatment (at any time) with total lymphoid irradiation or bone marrow transplantation.

The study commenced on September 16, 2025.

¹Van den Bergh PYK, et al. *Eur J Neurol*. 2021;28:3556-83.

vation of classical and lectin complement pathways.

The EMNERGIZE study (NCT07091630) will compare empasiprubart versus placebo in patients with CIDP. In this phase 3 study, ~160 adults will be randomized (2:1) to receive either intravenous empasiprubart or placebo on Days 1 and 8, then once every 4 weeks in a 24-week double-blind treatment period (Part A). Part A will be followed by a 4-week double-blind rollover and a 23-month open-label period (Part B), and a 15-month safety follow-up after the last dose (Figure).

The primary endpoint is a reduction of ≥ 1 -point versus baseline in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score at Week 24. Key secondary endpoints include changes from baseline at Week 24 in Inflammatory Rasch-built Overall Disability Scale score, Medical Research Council Sum score, dominant hand grip strength, and Timed Up and Go, and time to reduction of ≥ 1 point versus baseline in aINCAT score.

This phase 3 study will compare the efficacy and safety of empasiprubart versus placebo in patients with CIDP, focusing on functional ability, muscle strength/function, clinical status, gait impairment, and patient-reported outcomes.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P142 - Cod. 143292

EMPASIPRUBART VS IMMUNOGLOBULIN IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: EMVIGORATE PHASE 3 STUDY DESIGN

Doneddu P.E.^{*1}, Rinaldi S.², Brannagan T.H.³, Gable K.L.⁴, Stettner M.⁵, Van De Steen O.⁶, Budding K.⁶, Van De Walle I.⁶, Ellor S.⁶, Markov M.⁶, Allen J.A.⁷

¹ Neuromuscular and Neuroimmunology Unit, IRCCS Humanitas Research Hospital, 20089 Rozzano and Humanitas University, 20072

Pieve Emanuele, Milan, Italy, ² University of Oxford, Oxford, UK, ³ Vagelos College of Physicians & Surgeons, Columbia University Irving Medical Center, Columbia University, New York, United States of America, ⁴ Duke University Medical Center, Durham, United States of America, ⁵ University Medicine Essen, Essen, Germany, ⁶ argenx, Ghent, Belgium, ⁷ University of Minnesota, Minneapolis, United States of America

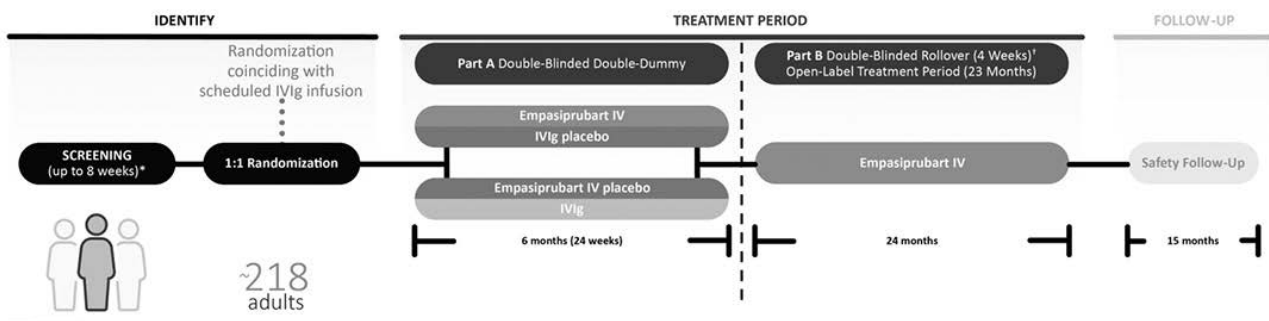
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a rare, immune-mediated neuropathy characterized by progressive muscle weakness and sensory dysfunction. The complement system plays a key role in promoting macrophage-mediated demyelination. Empasiprubart binds C2, blocking activation of classical and lectin complement pathways.

EMVIGORATE (NCT06920004) will compare intravenous (IV) empasiprubart and IV immunoglobulin (IVIg) in CIDP. In this phase 3, double-dummy study, ~218 adults on stable maintenance IVIg will be randomized to receive either empasiprubart IV or continue the stable IVIg dose in a 24-week double-blind treatment period (Part A), followed by a 24-month open-label period (Part B) and a 15-month safety follow-up (Figure). In Part A, participants will receive either empasiprubart IV plus IVIg placebo or empasiprubart IV placebo plus IVIg. In Part B, all participants will receive empasiprubart IV, while IVIg treatment will not be permitted. No study treatment will be administered during the safety follow-up period.

The primary endpoint is the percentage of participants achieving ≥ 1 -point improvement versus baseline in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score at Week 24. Secondary endpoints (Week 24) include changes from baseline in Inflammatory Rasch-built Overall Disability Scale score, Medical Research Council sum score, dominant hand grip strength and Timed Up and Go, time to decrease of ≥ 1 point in aINCAT score, and Patient Global Impression of Change actual values.

This phase 3 study will compare the efficacy and safety of empasiprubart IV and IVIg in CIDP, focusing on functional ability, muscle strength/function, gait performance, and patient-reported outcomes.

Figure. EMVIGORATE Study Design



CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; EAN, European Academy of Neurology; IV, intravenous; IVIg, intravenous immunoglobulin; PNS, Peripheral Nerve Society.

*A diagnostic adjudication committee confirmed participant diagnosis. *Participants from the empasiprubart arm will receive placebo once to maintain the blind of Part A.

Empasiprubart will be given as loading doses on Days 1 and 8, followed by maintenance doses every 4 weeks.

Key inclusion criteria: Meets criteria for CIDP based on EAN/PNS Task Force CIDP guidelines, second revision²; has either typical CIDP or 1 of the following CIDP variants: motor CIDP (including motorpredominant CIDP), multifocal CIDP (also known as Lewis-Sommer syndrome), focal CIDP, or distal CIDP; has residual disability and active disease; responded to IVIg and demonstrated dose dependence within 5 years; receiving treatment with IVIg (within a standard optimal maintenance dosing regimen, with a minimum weekly IVIg dose of ≥ 0.125 g/kg body weight).

Key exclusion criteria: Meets the criteria for possible CIDP based on EAN/PNS Task Force CIDP guidelines, second revision²; sensory CIDP; other autoimmune diseases that may affect CIDP symptom assessments; polyneuropathy of other causes; clinical diagnosis of systemic lupus erythematosus; prior long-lasting immunosuppressive/immunomodulatory treatment; prior treatment (at any time) with total lymphoid irradiation or bone marrow transplantation.

The study commenced on August 22, 2025.

¹Van den Bergh PYK, et al. *Eur J Neurol*. 2021;28:3556-83.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P144 - Cod. 143457****GAIT ANALYSIS IN PATIENTS WITH ANTI-MAG NEUROPATHY AND TAILORED REHABILITATION STRATEGIES**

Tierro B.^{*1}, Lazzari V.², Contessa P.², Agostini M.³, Cagnetta S.³, Bassi M.³, Salvalaggio A.¹, Masiero S.⁴, Briani C.¹, Coraci D.⁴

¹ Neurology Unit, Department of Neuroscience, University of Padova, Padova, Italy, ² Rehabilitation Unit, Padova University Hospital, Padova, Italy, ³ Department of Neuroscience, University of Padova, Padova, Italy, ⁴ Department of Neuroscience, University of Padova, Rehabilitation Unit, Padova University Hospital, Padova, Italy

Anti-Myelin-Associated Glycoprotein (anti-MAG) antibody neuropathy is a rare, slowly progressive demyelinating peripheral neuropathy characterized by distal sensory deficits, ataxia, and gait instability, leading to impaired balance and reduced quality of life. Outcome measures used for other inflammatory neuropathies present limitations in anti-MAG neuropathy.

To investigate the association between clinical and instrumented evaluations of balance and motor function in patients with anti-MAG antibody neuropathy at baseline and after personalized rehabilitation. Twenty-eight patients (11 women, 17 men; mean age 73 ± 10 years) with confirmed anti-MAG neuropathy (mean disease duration 10,11 [4-19]) underwent baseline assessment, including instrumented stabilometry under four postural conditions (stable/unstable surface, eyes open/closed), gait analysis, and standardized clinical scales (Mini-BESTest, Tinetti, SPPB, WALK-12, SF-12). A subset of six patients completed a personalized rehabilitation program balance training during gait and quiet standing, with/without perturbation, plus optional lower limb strengthening over approximately 10 sessions. Correlations between changes in instrumental and clinical measures were analyzed.

Pre-treatment, patients exhibited increased centre of pressure (CoP) area and oscillations across all conditions. Post-treatment, reductions in CoP area on unstable surfaces were related to improvements in balance and mobility scores, stride length and gait speed.

Instrumented and clinical evaluations provide complementary information in anti-MAG antibody neuropathy. Tailored rehabilitation program helped improve stability of patients ameliorating also quality of life. A focused gait assessment may improve understanding of balance impairments, monitor disease progression, and guide personalized rehabilitation strategies.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P146 - Cod. 143309****GUILLAIN-BARRE SYNDROME AND POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME: TWO CASES OF A RARE ASSOCIATION**

D'Apolito M.^{*}, Di Iasi G., D'Alessio A., Apice G., Renna R.

UOC Neurologia e Stroke Unit, AORN San Pio Benevento, Benevento, Italy

Posterior Reversible Encephalopathy Syndrome (PRES) and Guillain Barré syndrome (GBS) are rare and potentially life-threatening neurological conditions. We report the co-occurrence of PRES and GBS in 2 patients.

A 78 years old man presented to the emergency department for ongoing seizures. He presented gait disturbance with falls in the previous week. Brain MRI showed a picture suggestive of PRES. Aggressive iv antihypertensive and antiseizure therapy were started. The next day a rapidly progressive strength deficit in the 4 limbs became evident. Electroneurographic examination (ENG) documented an acute inflammatory demyelinating polyneuropathy (AIDP), therefore treatment with Iv immunoglobulins (Igs) was started. Clinical picture rapidly worsened with respiratory failure and the need for orotracheal intubation in intensive care unit. After Ig treatment, extubation was possible and the patient showed a progressive recovery of the strength deficit.

The second case is a 60 years old woman who presented with balance disorder and a flu like syndrome in the previous week. Lumbar puncture do not revealed albumin-cytological dissociation. ENG was normally but iv Igs was started. In the next hours, the clinical condition worsened with severe tetraparesis, bilateral ophthalmoplegia and VII, IX, and X nerve palsies. She was ataxic and hyporeflexic with power of 3/5 in all limbs. Brain MRI showed a picture suggestive of PRES with left parieto-occipital subarachnoid hemorrhage. ENG after 5 days was suggestive for AIDP. Patient progressively recovered, then was transferred in the Rehabilitation ward.

The relationship between PRES and GBS is not better explained.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P148 - Cod. 143296****LONG-TERM EFFICACY OF SUBCUTANEOUS EFGARTIGIMOD PH20 IN PATIENTS WITH CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: INTERIM RESULTS FROM THE ADHERE+ STUDY**

Armaroli A.^{*1}, Allen J.², Lin J.³, Stettner M.⁴, Gupta J.¹⁷, Gwathmey K.⁵, Istas G.¹, De Roeck A.¹, Kuwabara S.⁶, Lauria G.⁷, Querol L.⁸, Suresh N.⁹, Karam C.¹⁰, Skripuletz T.¹¹, Rinaldi S.¹², Echaniz--Laguna A.¹³, Van Hoorick B.¹, Yamasaki R.¹⁴, Van Doorn P.¹⁵, Lewis R.¹⁶

¹ argenx, Ghent, Belgium, ² University of Minnesota, Minneapolis, United States of America, ³ Huashan Hospital, Fudan University, Shanghai, China, ⁴ University Medicine Essen, Essen, Germany, ⁵ Virginia Commonwealth University, Richmond, United States of America, ⁶ Graduate School of Medicine, Chiba University, Chiba, Japan, ⁷ Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Neurologico Carlo Besta, Milan, Italy, ⁸ Hospital de La Santa Creu I Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, ⁹ Lakeland Regional Health, Lakeland, United States of America, ¹⁰ University of Pennsylvania, Philadelphia, United States of America, ¹¹ Hannover Medical School, Hanover, Germany, ¹² University of Oxford, Oxford, United Kingdom, ¹³ French National Reference Center for Rare Neuropathies (CERAMIC), Bicêtre University Hospital, Le Kremlin-Bicêtre, France, ¹⁴ Kyushu University Hospital, Fukuoka, Japan, ¹⁵ Erasmus University Medical Center, Rotterdam, Netherlands, ¹⁶ Cedars-Sinai Medical Center, Los Angeles, United States of America, ¹⁷ Duke University,

Durham, United States of America

The multi-stage, double-blinded, placebo-controlled ADHERE (NCT04281472) and open-label extension ADHERE+ (NCT04280718) trials assessed the efficacy and safety of subcutaneous (SC) efgartigimod PH20 in participants with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Enrolled participants with active CIDP (off treatment or CIDP treatments withdrawn during ≤ 12 -week run-in) received open-label, weekly efgartigimod PH20 SC 1000 mg (stage-A). Responders were randomized (1:1) to efgartigimod or placebo for ≤ 48 weeks (stage-B). Participants with clinical deterioration in stage-B or who completed ADHERE could enter ADHERE+ (weekly efgartigimod). Changes from run-in baseline (CFB) in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT), Inflammatory Rasch-built Overall Disability Scale (I-RODS), and dominant hand grip strength (GS) scores to ADHERE+ Week 36 were assessed.

Assess the efficacy of efgartigimod PH20 SC in participants with CIDP in ADHERE+ (interim analysis, data cutoff: February 16, 2024). 322 participants entered stage-A; 221 were randomized in stage-B (111 efgartigimod, 110 placebo). 99% of eligible participants entered ADHERE+. At ADHERE run-in baseline (N = 191), mean (standard error [SE]) aINCAT, I-RODS, and GS scores were 4.0 (0.10), 47.9 (1.05), and 46.6 (1.75), respectively. At ADHERE+ Week 36 (N = 150), mean CFB (SE) in aINCAT, I-RODS, and GS scores were -1.2 (0.15) and 8.8 (1.46) points and 17.5 (2.02) kPa, respectively, representing clinically meaningful improvements. Additionally, half of the participants who experienced clinical deterioration (aINCAT) during ADHERE stage-B restabilized on efgartigimod PH20 SC as early as ADHERE+ Week 4. Interim results from ADHERE+ indicate long-term effectiveness of efgartigimod PH20 SC in clinical outcomes in participants with CIDP.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P150 - Cod. 143273****MAGNITUDE OF RESPONSE WITH SUBCUTANEOUS EFGARTIGIMOD PH20 IN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY: ADHERE/ADHERE+ TRIALS**

Armaroli A.¹, Allen J.A.², Lewis R.A.³, Querol L.⁴, Eggers C.⁵, Kuwabara S.⁶, Hussain Y.M.⁷, Gwathmey K.G.⁸, Guptill J.T.¹¹, Ista G.¹, Van Hoorick B.¹, De Roeck A.¹, Basta I.⁹, Van Doorn P.A.¹⁰

¹ argenx, Ghent, Belgium, ² University of Minnesota, Minneapolis, United States of America, ³ Cedars-Sinai Medical Center, Los Angeles, United States of America, ⁴ Hospital de La Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain, ⁵ Kepler University Hospital, Johannes Kepler University, Linz, Austria, ⁶ Graduate School of Medicine, Chiba University, Chiba, Japan, ⁷ Austin Neuromuscular Center, Austin, United States of America, ⁸ Virginia Commonwealth University, Richmond, United States of America, ⁹ University Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia, ¹⁰ Erasmus MC, University Medical Center, Rotterdam, Netherlands, ¹¹ Duke University, Durham, United States of America

The ADHERE (NCT04281472) and open-label extension ADHERE+ (NCT04280718) trials assessed the efficacy and safety of subcuta-

neous (SC) efgartigimod PH20 in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Participants with active CIDP (off-treatment or standard treatments withdrawn during ≤ 12 -week run-in period) received weekly efgartigimod PH20 SC 1000 mg (stage-A). Responders were randomized to weekly efgartigimod or placebo (stage-B). Participants with clinical deterioration in stage-B or who completed ADHERE could enter ADHERE+ (weekly efgartigimod). Endpoints included changes in adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) and Inflammatory Rasch-built Overall Disability Scale (I-RODS) scores, and safety.

Assess the magnitude of response with efgartigimod PH20 SC in ADHERE/ADHERE+.

Improvement in mean aINCAT scores from ADHERE run-in baseline to stage-B baseline in participants receiving efgartigimod (n = 97) was maintained up to ADHERE+ Week 24 (n = 86). Mean aINCAT scores deteriorated in participants receiving placebo in ADHERE stage-B (n = 94); efgartigimod treatment in ADHERE+ reversed this deterioration. Overall, 60.8% (n = 59), 34.0% (n = 33), 22.7% (n = 22), and 11.3% (n = 11) of participants experienced improvements of ≥ 1 , ≥ 2 , ≥ 3 , and ≥ 4 points in aINCAT scores from run-in baseline to stage-B best improvement, respectively. Similarly, 48.5% (n = 47), 35.1% (n = 34), 30.9% (n = 30), and 24.7% (n = 24) of participants experienced improvements of ≥ 4 , ≥ 8 , ≥ 12 , and ≥ 16 points in I-RODS score from run-in baseline to stage-B best improvement, respectively. Efgartigimod across ADHERE/ADHERE+ was generally well-tolerated; treatment-emergent adverse events were mild/moderate in severity. Participants receiving efgartigimod demonstrated clinically meaningful improvements in aINCAT and I-RODS scores during ADHERE; improvements in aINCAT were maintained through ADHERE+ Week 24.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES**Abstract P152 - Cod. 143221****NERVE ULTRASOUND PICTURE IN AUTOIMMUNE NODOPATHIES: A CASE SERIES**

Tuccillo F.³, Emanuele C.¹, Tozza S.², Ricciardi D.³, Di Sarno I.², Fasolino A.³, Fiumarella R.², Fiore M.², Francesco H.³, Erra C.³

¹ Ospedale del Mare, UOC Neurologia, Stroke Unit, Napoli, Italy, ² Department of Neuroscience, Reproductive and Odontostomatological Science, University of Naples Federico II, Napoli, Italy, ³ AORNA Cardarelli, Clinical Neurophysiology Unit, Naples, Italy

Autoantibodies against nodal and paranodal proteins, including neurofascin155 (NF155), neurofascin186 (NF186), contactin-1 (CNTN1), and contactin-associated protein-1 (CASPR1), define a subgroup of immune-mediated neuropathies distinct from chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). These disorders, termed autoimmune nodopathies (AN), show reduced conduction velocity at nerve conduction studies without true segmental demyelination on pathology, likely due to disruption of the nodal architecture and impaired saltatory conduction. While nerve ultrasound (US) is a recognized supportive tool in CIDP, its role in AN remains poorly characterized.

We describe nerve US features of three patients with AN (two anti-NF155 positive and one anti-CASPR1 positive) recruited from tertiary

neuromuscular centers who underwent clinical, electrophysiological, and ultrasound evaluation.

US was performed on median, ulnar, tibial, fibular, and sural nerves and on C5–C7 roots bilaterally. Cross-sectional area (CSA) was measured at predefined sites, and enlargement pattern and fascicular variability were assessed.

All patients had a chronic disease course with good response to rituximab. Nerve US demonstrated increased CSA of nerve trunks, predominantly affecting proximal upper-limb segments and cervical roots. Enlargement was homogeneous, with a disto-proximal gradient, absence of focal thickening, and increased intranerve fascicular size variability.

Our findings suggest that AN presents a distinctive ultrasound pattern characterized by proximal, diffuse nerve enlargement rather than focal or multifocal changes typical of CIDP. Nerve US may aid in the differential diagnosis of neuropathies, particularly in patients with demyelinating features and poor response to conventional therapies. Larger studies are needed to confirm these observations.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P154 - Cod. 142841

NEUROPHYSIOLOGICAL AND ULTRASONOGRAPHIC ASSESSMENT TO IMPROVE DIFFERENTIAL DIAGNOSIS IN MADSAM AND MMN

Ricciardi D.*, Erra C., Della Valle P., Matrone F., Fasolino A., Tuccillo F., Habestwallner F.
UOC Neurofisiopatologia AORN Cardarelli Napoli, Napoli, Italy

CIDP and MMN are rare peripheral nerve diseases with a suspected autoimmune etiology. Despite several published diagnostic criteria, EAN/PNS criteria are the most widely used for both diseases, with high sensitivity and specificity. Neurophysiological assessment is mandatory for both diagnostic criteria sets, but there are many grey areas. Ultrasonographic assessment may be helpful in certain cases. To date, it is unclear how to use neurophysiological/ultrasonographic data to differentiate classic CIDP from its variants, or the multifocal CIDP variant from MMN.

We conducted a retrospective data analysis on CIDP and MMN patients followed at our neuromuscular disease center.

We identified 15 patients with a MADSAM CIDP variant and 6 patients with MMN. Our study revealed that many patients initially diagnosed with MADSAM or MMN were re-classified following a comprehensive neurophysiological assessment. The ultrasonographic approach does not help distinguish the two multifocal diseases. Evoked somatosensory potentials, H-reflex, and extensive sensory conduction studies are valuable tools for refining the differential diagnosis of these rare peripheral nerve diseases.

Our study underscores the need for greater clarity in the EAN/PNS diagnostic criteria for CIDP and MMN, particularly regarding the use of neurophysiological assessment to differentiate CIDP multifocal variants from MMN.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P156 - Cod. 143002

OVERLAPPING AUTOIMMUNE NEUROMUSCULAR DISORDERS: A CASE OF MYASTHENIA GRAVIS AND ANTI-HMGCR NECROTIZING MYOPATHY

Sogus E.¹, Paola D.², Cardellini D.², Alessandra V.², Giopato F.², Rigoni M.T.², Bonifati D.M.*²

¹ University of Padua, Padua, Italy, ² Unit of Neurology, Ca' Foncello Hospital

The coexistence of myasthenia gravis (MG) and immune-mediated necrotising myopathy (IMNM) is rare and can pose a significant diagnostic challenge, particularly when clinical features overlap.

To describe a rare case of overlapping of myasthenia gravis (MG) and immune-mediated necrotising myopathy (IMNM) with anti-HMG-CoA reductase antibodies.

We report the case of a 72-year-old patient exposed to statins who presented with progressive weakness of the proximal limbs, exercise intolerance, and bulbar symptoms, including dysphagia, masticatory fatigue, and hypophonia. Statins had been discontinued prior to referral due to muscle symptoms. Neurological examination revealed fluctuating weakness with fatigability, while laboratory tests showed marked hyperCKemia. Electromyography showed a mixed myopathic and neurogenic pattern, while repetitive nerve stimulation revealed a decremental response. Serological tests revealed high titres of anti-acetylcholine receptor antibodies and anti-HMG-CoA reductase antibodies, while anti-MuSK antibodies were negative. Chest CT excluded thymic pathology.

Although the clinical picture was initially consistent with generalised MG, the persistence of proximal weakness and elevated creatine kinase levels prompted further investigation, leading to the diagnosis of concomitant immune-mediated necrotising myopathy. Immunosuppressive treatment and symptomatic therapy led to progressive clinical improvement, normalisation of creatine kinase levels, and sustained drug-induced remission of both conditions.

This case highlights the importance of recognising overlapping autoimmune neuromuscular disorders in patients with MG and atypical laboratory or electrophysiological findings. Accurate diagnosis allows for more personalised clinical monitoring, appropriate interpretation of disease fluctuations, and timely therapeutic adjustments during long-term follow-up.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P158 - Cod. 143298

PROGNOSTIC FACTORS IN GUILLAIN-BARRÉ SYNDROME: A RETROSPECTIVE COHORT STUDY IN A TERTIARY REFERRAL CENTRE

Russo M.*, De Luca M., Toscano A., Rodolico C., Mazzeo A., Messina S.
University of Messina, Messina, Italy

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy and early identification of prognostic indicators is essential to optimize therapeutic strategies and management.

We aimed to identify the association of clinical, neurophysiological and laboratory parameters with functional outcome at 6 months. We also evaluated the response to immunomodulatory treatments among different subtypes. We performed a single-center, retrospective observational study on patients consecutively admitted between 2015 and 2024 in a tertiary referral centre. Functional disability, muscle strength and autonomic symptoms were assessed using the Hughes Functional Grading Scale (HFGS), the Medical Research Council (MRC) sum score and the COMPASS-31 questionnaire. Neurophysiological and laboratory parameters were analyzed.

We included 50 patients (mean age at onset of 56, SD:19 yrs, M:F, 58% vs 42%). The clinical severity at admission was high [(HFGS score of 4 (IQR 3–4)]. Twenty-eight percent of patients exhibited dysphagia and 20% required ventilatory support. COMPASS-31 score was 23, SD:12. The average time from symptom onset to specific therapy was 7.5, SD:4 days. Neurofilament light chain (NfL) levels in CSF were 470.8 pg/mL, SD:378.1.

The factors found to be associated with an unfavourable outcome (HFGS > 3 at 6 months) were: age > 60 years ($p = 0.03$), HFGS > 4 at admission ($p = 0.01$), time from onset to therapy > 7 days ($p = 0.04$), serum sodium < 136 mmol/L ($p = 0.04$), and NfL levels > 500 pg/mL ($p = 0.02$).

This real-world study confirms the heterogeneity of GBS and supports the value of a multidimensional assessment to improve prognostic stratification.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P160 - Cod. 142979

RISK OF FALSE ANTI-MAG ANTIBODY POSITIVITY BY ELISA BUHLMANN ASSAY IN CLINICAL PRACTICE

Lozi C.*, De Lorenzo A., Cutellè C., Terenghi F., Gallo C., Nobile--Orazio E., Doneddu P.

Humanitas Research Hospital, Neuromuscular and Neuroimmunology Unit, Milano, Italy

ELISA Bühlmann is the gold standard for anti-MAG neuropathy diagnosis, and false anti-MAG positivity is generally considered rare.

To assess the positive predictive value (PPV) of ELISA Bühlmann and the risk of false anti-MAG positivity in patients with suspected anti-MAG antibody neuropathy. We retrospectively identified consecutive patients at our center who underwent clinically indicated anti-MAG testing and had antibody titers $\geq 1,000$ BTU. False positivity was defined as the presence of a physician-established alternative diagnosis incompatible with the anti-MAG neuropathy phenotype.

Among 68 anti-MAG-positive patients, 13 (19%) were diagnosed with conditions other than anti-MAG neuropathy (PPV 81%), including CIDP ($n = 4$), cryoglobulinemia ($n = 1$), meralgia paresthetica ($n = 1$), Morton neuroma ($n = 1$), vasculitic neuropathy ($n = 1$), and idiopathic bilateral brachial plexopathy ($n = 1$). In these patients, anti-MAG titers ranged from 3,300 to 77,000 BTU. In four additional

patients, diagnostic uncertainty between anti-MAG neuropathy and CIDP persisted (BTU range: 15,000–70,000). Anti-MAG neuropathy was diagnosed in 55 patients (81%; BTU range: 4,156–140,000), all with distal sensory involvement. Four clinical phenotypes were identified: sensory ataxia with ($n = 28$) and without ($n = 9$) distal weakness, ataxia with proximal and distal weakness ($n = 10$), and isolated sensory symptoms ($n = 8$). Rituximab was effective in 76% cases, while IVIg in 7%. Neurophysiology demonstrated prolonged distal latencies in 95%.

ELISA Bühlmann testing is associated with a non-negligible rate of potential false positivity, even at high antibody titers. These findings indicate that anti-MAG ELISA results should not be interpreted in isolation but integrated with clinical and neurophysiological features to ensure diagnostic accuracy and appropriate treatment selection.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P162 - Cod. 143072

RITUXIMAB IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY

Sorrenti B.*¹, Cassano E.², Gallo C.³, Manganelli F.², Nobile--

Orazio E.³, Filippi M.¹, Previtali S.C.¹, Doneddu P.E.³, Falzone Y.M.¹

¹ *IRCCS Ospedale San Raffaele, Milano, Italy*, ² *Università di Napoli Federico II, Napoli, Italy*, ³ *IRCCS Humanitas Clinical and Research Center, Milano, Italy*

Rituximab is a B-cell depleting therapy increasingly used as a therapeutic option in CIDP patients. Nevertheless, its clinical effectiveness and optimal timing of administration remain uncertain.

To retrospectively collect and analyze clinical data from patients with CIDP treated with rituximab at three Italian centers.

Thirty-two patients were included. Mean age at diagnosis was 49.1 ± 21.3 years with a mean disease duration before rituximab initiation of 79.8 ± 78.6 months. Clinical phenotypes included typical CIDP (65.6%), multifocal (15.6%), distal (9.4%), sensory (6.3%) and motor (3.1%). Prior to rituximab, 27 patients (84.4%) had received first-line therapies (IVIg and/or corticosteroids), while 5 patients (15.6%) had been treated with second-line immunosuppressive therapies. Rituximab was mainly initiated due to inefficacy or partial response to first-line treatments, steroid dependence, or treatment-related adverse events. At baseline, mean MRC sum score was 49.9 ± 9.9 and mean INCAT disability score was 4.2 ± 2.0 . At 6 months, mean MRC and INCAT scores improved to 53.1 ± 7.9 and to 3.0 ± 2.1 , respectively ($p = 0.01$). Nineteen patients (65.5%) met the predefined criteria for clinical response, while 11 patients were non-responders. Among responders, rituximab was discontinued in 14 cases due to clinical remission or significant improvement. Nine patients received rituximab within 24 months from symptoms onset (early RTX); five of six evaluable patients were responders at 6 months, and most discontinued concomitant therapies. No baseline clinical or treatment-related variables were significantly associated with clinical response.

Rituximab may represent a therapeutic option in selected CIDP pa-

tients, though its long-term efficacy and optimal timing require further investigation.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P164 - Cod. 142941

SENSORY NEUROPATHY AND ALLODYNIA IN AN HIV-POSITIVE PATIENT WITH ERYTHEMA NODOSUM: A COMPLEX DIAGNOSTIC CASE

Vollaro A.F.M.*, Grandis M., Benedetti L., Gemelli C., Garneri M., Cabona C., Bavestrello G., Barone C., Benvenuto G., Trigiante M., Schenone A.

U.O. Neurologia, Università degli Studi di Genova, IRCCS Ospedale Policlinico San Martino, Genova, Italia, Genova, Italy

Peripheral neuropathy is a frequent neurological complication in people living with HIV, with a multifactorial pathogenesis including viral, toxic, infectious, and immune-mediated mechanisms. The association with inflammatory dermatological manifestations, such as erythema nodosum, raises suspicion for an underlying systemic inflammatory or vasculitic process and represents a diagnostic challenge. To describe a diagnostically complex case of peripheral neuropathy in an HIV-positive patient with concomitant erythema nodosum, and to highlight the diagnostic value of sural nerve biopsy in suspected immune-mediated vasculitic neuropathy when non-invasive investigations are inconclusive.

A 52-year-old woman with well-controlled HIV infection developed progressive distal sensory symptoms and severe lower-limb allodynia associated with painful nodular skin lesions.

Skin biopsy demonstrated septal panniculitis consistent with erythema nodosum. Nerve conduction studies revealed a mild sensory axonal neuropathy. An extensive diagnostic workup, including neuroimaging, cerebrospinal fluid analysis, immunological and infectious screening, and total-body CT, was non-diagnostic. Empirical corticosteroid therapy resulted in partial clinical improvement.

Sural nerve biopsy subsequently revealed necrotizing small-vessel vasculitis, confirming an immune-mediated vasculitic neuropathy and guiding therapeutic escalation.

This case highlights the diagnostic complexity of peripheral neuropathy in HIV-positive patients presenting with concomitant dermatological manifestations. Erythema nodosum may represent a marker of underlying systemic inflammatory disease. In selected cases, sural nerve biopsy remains a pivotal diagnostic tool, allowing accurate etiological classification and timely initiation of appropriate therapy.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P166 - Cod. 143267

THE JOURNEY TO DIAGNOSIS FOR PATIENTS WITH CIDP: RESULTS FROM A REAL-WORLD INTERNATIONAL SURVEY

Bonetto C.*¹, Brackx F.³, Arvin--Berod C.¹, Paci S.¹, Van De Veire L.³, Taylor Y.², Wright J.², Dewilde S.³

¹ *argenx, Ghent, Belgium*, ² *Adelphi Real World, Bollington, United Kingdom*, ³ *Services in Health Economics, Brussels, Belgium*

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a rare immune-mediated disorder marked by progressive or relapsing weakness and sensory impairment. Its heterogeneous clinical presentation, lack of a definitive diagnostic biomarker, and overlap with other neuropathies frequently lead to diagnostic delay and misdiagnosis. Delayed diagnosis may postpone appropriate treatment and negatively affect long-term outcomes. Real-world evidence describing diagnostic pathways can help identify factors associated with delayed diagnosis and inform strategies to improve early disease recognition.

Data were obtained from Adelphi's CIDP Disease Specific Programme™, a multinational, real-world, cross-sectional survey conducted between September 2022 and April 2023, including Italy. Neurologists provided demographic and clinical data for 542 patients with CIDP in routine practice. Time from symptom onset to confirmed diagnosis, misdiagnosis frequency, and factors associated with diagnostic delay were evaluated using descriptive analyses, chi-squared tests, and multivariable linear regression on log-transformed time to diagnosis.

The mean patient age was 54.0 years, and 62% were male. The median time from symptom onset to CIDP diagnosis was 7.0 months (interquartile range: 3.2–13.0). 37% of patients experienced at least one misdiagnosis prior to CIDP confirmation, most frequently GBS. Multivariable analyses showed that mild disease severity at symptom onset, CIDP variants, and prior misdiagnosis were independently associated with longer time to diagnosis, whereas patients with moderate or severe symptoms were diagnosed more rapidly.

CIDP diagnosis is frequently delayed in real-world practice, particularly among patients with mild or atypical presentations. Improving awareness of CIDP heterogeneity and optimizing diagnostic pathways may facilitate earlier diagnosis and improved patient outcomes.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P168 - Cod. 142837

VISUAL EVOKED POTENTIALS AND CHRONIC IDIOPATHIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: MAY VISUAL PATHWAY DYSFUNCTION BE UNDERDIAGNOSED?

Paola D.V.*, Ricciardi D., Erra C., Matrone F., Fasolino A., Tuccillo F., Habetswallner F.

1. Clinical Neurophysiology Unit, Cardarelli Hospital, Naples, Italy., Napoli, Italy

Visual pathway dysfunction in CIDP has been reported in up to 47% of patients. Still, to date, no clear association has been established between distinct disease variants.

In our study, we retrospectively investigated visual pathway dysfunction through visual evoked potentials. Thirty CIDP patients (15 with the Lewis-Sumner variant and 15 with the typical variant), fulfilling the EAN/PNS 2021 criteria, were recruited. Nerve conduction studies, MRI, clinical evaluation using standardized scales (I-RODS, MRC,

Incat disability scale, Incat sensory scale), and CSF were compared. Neurophysiological data (P100 latency and N75-P100 amplitude) were also compared with those of thirty healthy controls.

In the CIDP group, we found significant VEP abnormalities, characterized by low-amplitude potentials (N75-P100), and increased P100 latency ($p < 0.05$). Moreover, visus pathway dysfunction was predominant in the Lewis-Sumner group. In four patients, MRI detected demyelinating lesions in the CNS, one patient had a previous history of retrobulbar optic neuritis.

Visual evoked potential abnormalities may reflect increased susceptibility of visual pathways to immune-mediated injury, which can affect both the peripheral and central nervous systems in patients with CIDP.

INFLAMMATORY/DYSIMMUNE NEUROPATHIES

Abstract P170 - Cod. 143495

WHEN MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODIES EXTENDS BEYOND THE CENTRAL NERVOUS SYSTEM: AN ATYPICAL CLINICAL PRESENTATION

Colantuono P.^{*1}, Sacco S.¹, Ricci S.²

¹ Department of Biotechnological and Applied Clinical Sciences - University of L'Aquila, L'Aquila, Italy, ² Department of Neurology and Stroke Unit - "SS. Filippo e Nicola" Hospital, Avezzano, Italy

Myelin oligodendrocyte glycoprotein associated disease (MOG-AD) typically involves central nervous system (CNS), with an immune-mediated mechanism. Here, we present a rare manifestation of peripheral nervous system (PNS) involvement mediated by MOG antibodies. A 46 years old man, with no significant medical and family history, presented with paraesthesias in his feet after administration of COVID-19 vaccine. During the following two years he complained of bilateral dysesthesias in his feet and cramps in lower limbs.

On neurological examination the patient presented muscle fasciculations and brisk deep tendon reflex in lower limbs. Nerve conduction study showed demyelinating polyneuropathy while electromyography showed fasciculation potentials with no evidence of neurogenic damage. Spinal magnetic resonance imaging showed enhancement of medullary conus and cauda equina roots. Elevated cerebrospinal fluid protein level emerged at lumbar puncture. Absence of infectious or autoimmune antibodies, including anti-ganglioside, and paraneoplastic antibodies, was demonstrated. Positivity for MOG antibodies on serum was detected. The patient was diagnosed with radiculomyelitis associated to MOG antibodies and treated with intravenous steroids with marked improvement of symptoms.

MOGAD is an inflammatory disease of CNS. A few cases of radiculomyelitis associated to MOG antibodies have been described. In our patient, clinical, radiological and neurophysiological examinations led to the diagnosis. This rare phenotype can be due to the undefined line between the CNS and PNS at the transitional zone, where nerve roots contains astrocytes, oligodendrocytes, and central myelin, whilst they are well segregated elsewhere.

Our case underlines the importance of checking MOG antibodies in radiculomyelitis of uncertain cause.

NEUROPHYSIOLOGY AND PAIN

Abstract P236 - Cod. 142894

ANALGESIC POTENTIAL OF ALLOPREGNANOLONE IN MALE AND FEMALE MODELS OF BORTEZOMIB-INDUCED PERIPHERAL NEUROPATHY

Iseppon E.^{*1}, Tonelli E.¹, Fabbro V.¹, Chiorazzi A.¹, Canta A.¹, Alberti P.¹, Carozzi V.A.¹, Pozzi E.¹, Cherchi L.¹, Fermi S.¹, Segmani I.¹, Fantoni L.¹, Rodriguez--Menendez V.¹, Ballarini E.¹, Cavaletti G.¹, Distasi C.², Lym D.², Giatti S.³, Meregalli C.¹

¹ Università Milano-Bicocca, Dipartimento di Medicina e Chirurgia, Monza, Italy, ² Università del Piemonte Orientale, Dipartimento di Scienze Farmaceutiche, Novara, Italy, ³ Università degli Studi di Milano, Dipartimento di Scienze Farmacologiche e Biomolecolari "Rodolfo Paoletti", Milano, Italy

Proteasome inhibitor bortezomib (BTZ) causes painful peripheral neuropathy (BIPN) that hinders patients' quality of life. Currently, there has been little preclinical research investigating sexually dimorphic differences in BIPN or in the response to therapeutics. Therefore, identifying novel compounds with favorable safety profiles is essential to develop effective strategies. Several reports suggested that similar paradigms can be ameliorated by concomitant use of neuroactive steroids, cholesterol derivatives with proven neuroprotective effects. Therefore, we tested the analgesic potential of allopregnanolone (ALLO) in rodent models of BIPN. Female and male Wistar rats were intravenously treated with BTZ (0.2 mg/kg, 3qw) for 4 weeks together with subcutaneous co-administrations of BTZ and ALLO (3mg/kg) every other day. We investigated the efficacy of ALLO using a battery of behavioral and neurophysiological tests, morphometrical analyses of myelinated nerves and intraepidermal small unmyelinated fibers densities, and macrophage infiltration assays.

The development of BIPN in these animals was not dependent on their sex, since BTZ led to the development of neuropathy and allodynia in both males and females, and was similarly alleviated by ALLO. Moreover, BTZ induced significant loss of both myelinated and unmyelinated fibers in the caudal nerves and skin, respectively. ALLO successfully protected unmyelinated fibers from degeneration in both sexes.

Taken together, our results show that ALLO could represent a valuable tool to manage painful BIPN in the clinical setting for both sexes, paving the way for further testing of its therapeutic potential.

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NEUROPHYSIOLOGY AND PAIN

Abstract P238 - Cod. 143088

CARDIOVASCULAR AND SYMPATHETIC REACTIVITY DURING MENTAL STRESS IN HYPOCRETIN-DEFICIENCY NARCOLEPSY: A MICRONEUROGRAPHIC STUDY

Furia A.^{*1}, Pizza F.¹, Plazzi G.², Liguori R.¹, Donadio V.¹

¹ *Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy,* ² *Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy*

Mental stress induces an arousal reaction and a subsequent response on various physiological parameters. Previous studies with microneurography, a neurophysiological technique registering small fiber activity such as muscle sympathetic nerve activity (MSNA), have shown that individuals with inhibited MSNA after arousal ("responders") showed a lesser blood pressure (BP) response when compared to "non-responders". Hypocretin relates to arousal activation but no data has been reported in hypocretin-deficiency narcolepsy with cataplexy (NC) patients. This study may clarify if hypocretin is involved in cardiovascular and sympathetic activities changes during arousal. 15 male patients with NC (aged 37 ± 11 years) and 15 male healthy controls (aged 36 ± 11 years) were subjected to microneurography of the peroneal nerve and concomitant recording of respiratory movements, blood pressure and electrodermal activity. Responders and non-responders were defined as above. All individuals were recorded at rest, after mental stress and after cold stimulation. BP variation was analyzed between NC patients and healthy controls, as well as responders vs non-responders between groups.

3 NC patients and 3 healthy controls could be classified as responders, thus showing no difference. As expected, mental stress induced a BP increase which was less elevated in responders, both in the NC and in the healthy control group.

In this study, wake NC patients showed no significant difference in BP and MSNA responses to arousal and stress compared to controls. This study does not support a major role of hypocretin in regulating cardiovascular and sympathetic reactivity to arousal and mental stress.

NEUROPHYSIOLOGY AND PAIN

Abstract P240 - Cod. 143178

CLINICAL FEATURES DISTINGUISHING FIBROMYALGIA FROM SMALL FIBER NEUROPATHY

Masciarelli F.^{*1}, Dell'Aversana D.¹, Vitale F.¹, Ciccarelli G.¹, Manganelli F.¹, Caporaso G.², Provitera V.², Nolano M.¹

¹ *Department of Neurosciences, Reproductive Sciences and Odontostomatology, University Federico II of Naples, Naples, Italy, Napoli, Italy,* ² *UOC Medical Genetics, IRCCS Foundation - Casa Sollievo della Sofferenza, Viale Cappuccini snc, 71013 San Giovanni Rotondo (FG), Italy, Telesse, Italy*

Fibromyalgia syndrome (FMS) has been described associated with small fiber pathology and it manifests with a distinct clinical picture compared with pure small fiber neuropathy (SFN). However, some severe fibromyalgic patients may present with overlap phenotypes. We compared sensory and autonomic symptoms and signs across FMS, FMS associated with SFN and pure SFN.

We retrospectively analyzed 115 patients with FMS and 67 with biopsy-confirmed SFN without FMS. Within FMS, 91 patients were classified as FMS+SFN, when associated with SFN symptoms and signs, otherwise as FMS (n = 24).

We collected pain descriptors and distribution, sensory signs (allodynia, hyperalgesia, hypoesthesia to pinprick/touch), autonomic symptoms and comorbidities.

Our population (mean age 46.1 ± 14.3 years) was mainly composed of women (FMS+SFN 90.1%; FMS 79.2%; SFN 68.7%). Compared with FMS, FMS+SFN more often reported burning pain (91.2% vs 58.3%), hyperalgesia (23.1% vs 0%) and allodynia (47.3% vs 0%) and less frequently was associated with dysmetabolic comorbidities (15.4% vs 37.5%). Compared with SFN, FMS+SFN more frequently reported excruciating pain (91.2% vs 67.2%), painful cold (19.8% vs 7.5%), pins and needles (19.8% vs 7.5%), tingling (54.9% vs 32.8%), pinprick hyperalgesia (23.1% vs 3.0%), mechanical allodynia (47.3% vs 29.9%), itch (65.9% vs 38.8%), hypoesthesia to pinprick (82.4% vs 54.0%) and widespread pain distribution (95.6% vs 40.2%). Overall, FMS+SFN presented more frequently autonomic symptoms (mostly urinary) and autoimmune comorbidities.

Patients with FMS/SFN phenotype overlap show a more severe sensory/autonomic burden than FMS and should prompt evaluation for the search of potentially treatable causes.

NEUROPHYSIOLOGY AND PAIN

Abstract P242 - Cod. 143377

ELECTRODIAGNOSTIC CLASSIFICATION OF SENSORY NEUROPATHIES: SEVERITY CLUSTERS AND CLINICAL CORRELATES

Bosco L.¹, Laurini C.¹, Angelini L.¹, Bosco M.², Ratti A.^{*1}, Schito P.¹, Russo T.¹, Sorrenti B.¹, Strano C.M.M.¹, Butera C.¹, Falzone Y.M.¹, Previtali S.¹, Filippi M.¹, Del Carro U.¹

¹ *Department of Neurology, IRCCS Ospedale San Raffaele, Milan, Italy, Milano, Italy,* ² *Azienda ULSS n.2 "Marca Trevigiana", Regione Veneto, Treviso, Italy*

Sensory neuropathies with large-fiber involvement show wide etiologic and electrophysiological heterogeneity. We aimed to derive an objective ENG-based severity classification to provide a shared vocabulary and support clinical decision-making.

To retrospectively analyze nerve conduction studies performed at IRCCS San Raffaele Hospital between September 2018 and September 2024, extracting double-pseudonymized data from clinical reports. Adult studies with isolated sensory involvement were identified using sural sensory nerve action potential (SNAP) amplitude thresholds after exclusion of motor abnormalities. Unsupervised clustering used Gower dissimilarities of sural and "best" upper-limb (UL) SNAP amplitudes (percentage of lower limit of normal) plus absence flags. Among 15,744 consecutive examinations, 308 met inclusion criteria. Three well-separated ENG severity classes emerged: mild (reduced but present sural and present UL SNAPs), moderate (absent sural, present UL SNAPs), and severe (absent sural and UL SNAPs). Clinical severity increased monotonically across classes. Severe cases were younger than mild and moderate cases (53.5 vs 64.0 and 62.5 years, respectively) and more disabled (mRS ≥ 2 : 50.0% in severe vs 30.4% in moderate vs 16.2% in mild). Etiologic profiles differed: the severe class was enriched in paraneoplastic (12.5%) and genetic (40.6%) causes, with CANVAS accounting for one in four cases.

By stratifying patients based on SNAP amplitudes, we identified a differential etiologic enrichment rather than a continuum of disease progression. Severe electrophysiology with motor sparing should prompt RFC1 testing and immune/paraneoplastic work-up, whereas in mild to moderate cases diabetes is the most common cause, with many cases remaining idiopathic.

NEUROPHYSIOLOGY AND PAIN

Abstract P244 - Cod. 142772

FOCAL ACQUIRED NEUROMYOTONIA IN ISOLATED NEUROGENIC HYPERTROPHY: A STRANGE CASE OF ISOLATED CALF SWELLING

Gallo C.*², Terenghi F.², Maderna L.¹, Nobile Orazio E.²

¹ 2 Department of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, P-Brescia 20, 20149, Milano, Italy, ² 1 Neuromuscular and Neuroimmunology Unit, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089 Rozzano – Milan, Italy

Neuromyotonia consist in continuous peripheral nerve hyperexcitability, manifesting as myokymia, cramps, impaired muscle relaxation. It's characterized by high-frequency (150–250 Hz), decrementing, repetitive discharges of single motor units, known as neuromyotonic discharges. They are most commonly associated with acquired autoimmune etiologies, such as Isaacs syndrome, but may also occur in chronic disorders affecting nerves or muscles.

We report the case of a 38-year-old man presenting with history of painful swelling of the right calf, nocturnal cramps, focal muscle twitching. His medical history was notable for neurosurgical treatment of a large L5–S1 disc herniation at age 36.

CPK levels were moderately elevated, Caspr2 and LGI1 antibodies were negative. Neurological examination revealed isolated hypertrophy of posterior compartment of the right leg with preserved strength, but difficultly running and hopping. EMG demonstrated chronic neurogenic changes in S1-innervated distal muscles, denervation and florid neuromyotonic discharges. Muscle MRI confirmed hypertrophy of right calf, without edema or contracture on ultrasound. Antiepileptic drugs and a cycle of intravenous immunoglobulin were ineffective. A diagnosis of focal neurogenic muscle hypertrophy (F-NMH) secondary to S1 root injury was suspected. Muscle biopsy was proposed, highlighting possible overlap with focal neurogenic myositis; botulinum toxin injection was considered for symptomatic relief.

Focal neuromyotonia is a rare manifestation of radiculopathy and is even less frequently associated with muscle hypertrophy. Symptoms may persist despite surgical decompression. Although immunomodulatory therapy and sodium channel-blocking agents are often beneficial, botulinum toxin or surgical approaches may be required. Careful clinical history and expert electrophysiological evaluation are crucial for accurate diagnosis.

NEUROPHYSIOLOGY AND PAIN

Abstract P246 - Cod. 143089

SMALL FIBER NEUROPATHY ASSOCIATED TO COVID INFECTION: AN UPDATE

Furia A.*¹, Incensi A.², Giannoccaro M.P.¹, Morelli L.¹, Ricciardiello F.², Rizzo G.², Liguori R.¹, Donadio V.¹

¹ Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna, Italy, ² Istituto delle Scienze Neurologiche di Bologna, UOC Clinica Neurologica, Bologna, Italy

Small Fiber Neuropathy (SFN) has been shown to be the underlying cause in part of patients with “long COVID syndrome”. The aim of this study is to expand upon the previous findings of our study on patients who developed SFN following COVID infection, particularly focusing on prognosis.

Patients presenting with signs and symptoms suggestive of SFN < 2 months following COVID infection and/or vaccination were prospectively recruited. Patients underwent full examination, and skin biopsy for quantitation of intraepidermal small nerve fiber density (IENFD). Congruently with Besta criteria, SFN was diagnosed in presence of a congruent clinical picture and reduced IENFD at distal leg. Patterns of symptom distribution, autonomic involvement and additional symptoms (itch, myalgia-like pain) were determined. Patients were reassessed > 24 months from onset, in order to assess evolution of SFN symptomatology.

Out of 82 patients, 73 fulfilled SFN diagnosis. Onset time was at a median of 30 days (range 10-60) after COVID infection/vaccination. 24 of these patients (30%) presented with non-length dependent signs and symptoms, while itch (11, 15%) and myalgia-like pain (13, 18%) were less represented. After follow-up visits, 44 patients (60%) reported subjective improvement, 22 (30%) stability, and 7 reported worsening of SFN symptomatology.

SFN can be a relevant, albeit unrecognized, component of the long COVID syndrome. A significant proportion of patients can present with atypical distribution of signs and symptoms, possibly hindering prompt diagnosis. In this studied cohort, most patients reported subjective improvement at follow-ups, suggesting the need of long-time evaluations.

FRIDAY, MAY 15TH, 2026

POSTER SESSION MYOPATHIES | even numbers

15:00-16:30

Chairs: Angela Berardinelli, Gaia Scarpini

BASIC MYOLOGY

Abstract P004 - Cod. 143373

CELLULAR MODEL FOR 2D IN VITRO MUSCLE DIFFERENTIATION

Sian V., Sarparanta J., Jonson P.H., Hackman P., Udd B., Savarese M.*

Folkhälsan Research Center, Helsinki, Finland

Optimizing cellular models for muscle differentiation is essential for investigating the mechanisms underlying myogenesis and muscle disease. However, obtaining primary myoblasts from patients and healthy donors presents ethical and procedural challenges, and primary cell cultures often suffer from limited feasibility and reproducibility. Among the most widely used systems, the murine C2C12 cell line remains a standard in vitro model for skeletal muscle research. We aimed to optimize in vitro differentiation conditions for C2C12 cells cultured on ultra-compliant gelatin hydrogels for up to three weeks. In parallel, we sought to standardize and further characterize L6 rat myoblasts as a complementary model to C2C12, particularly for metabolic studies.

DMEM supplemented with 2% horse serum and 10% Opti-MEM (DMO) supported robust myotube formation, yielding thin, aligned, and contractile myofibres from C2C12 myoblasts. Supplementation with insulin and pyruvate further enhanced myotube maturation. RNA sequencing confirmed progressive transcriptional reprogramming consistent with myogenic differentiation. L6 myotubes exhibited insulin-responsive glucose uptake, highlighting their suitability for investigating insulin signalling and glucose transport. These cells displayed a gene expression profile enriched in metabolic pathways, with less pronounced activation of muscle function- and contraction-related genes.

Although 2D in vitro systems do not fully recapitulate native muscle complexity, C2C12 and L6 cultures remain cost-effective, scalable, and reproducible experimental tools. Beyond structural and metabolic analyses, these models are particularly valuable for studying the epigenetic regulation of myogenesis, including chromatin remodeling, histone modifications, and nuclear architecture, as well as for epigenetic drug screening and evaluating therapeutic strategies targeting nuclear organization and gene regulation.

BASIC MYOLOGY

Abstract P006 - Cod. 142944

DIAGNOSTIC ACCURACY OF QUANTITATIVE ELECTROMYOGRAPHY IN IDIOPATHIC INFLAMMATORY MYOPATHIES: A COMPARATIVE ANALYSIS WITH MUSCLE BIOPSY

Lasorella P.¹, Zoppi D.*², Russo A.², Vallefucio F.², De Maria M.², Russo R.², Boemia V.², Marciano E. Ortolano A.³, Somma T.³, Ruggiero L.²

¹ *Presidio Ospedaliero "Lorenzo Bonomo", Andria (BT), Italy,* ² *Department of Neurosciences, Reproductive Sciences, and Odontostomatology, University of Naples "Federico II", Napoli, Italy,* ³ *Department of neurosciences, reproductive and Odontostomatological sciences, division of neurosurgery, university of Naples "Federico II", Napoli, Italy*

Idiopathic inflammatory myopathies (IIM) are heterogeneous disorders typically diagnosed and subclassified via muscle biopsy. While biopsy is the gold standard, it is invasive and prone to sampling errors. Quantitative electromyography (qEMG) offers a minimally invasive alternative for assessing motor unit characteristics and muscle membrane instability, but its correlation with histopathological findings has not been fully established. Defining the diagnostic performance of qEMG and its correlation with biopsy findings could improve the accuracy and reliability of the neurophysiological evaluation in patients with suspected inflammatory myopathy.

We retrospectively evaluated 40 patients with IIM and 20 pathological controls (non-inflammatory myopathy). All subjects underwent qEMG (tibialis anterior, rectus femoris, biceps brachii) and muscle biopsy. qEMG parameters included Motor Unit Potentials (MUPs) duration, interference pattern, and fibrillation. Histological damage was assessed using a standardized scoring system.

qEMG identified a myogenic pattern (reduced MUPs duration) in 35% of biceps brachii, 32.5% of rectus femoris, and 27.5% of anterior tibialis. Fibrillation was significantly more prevalent in the IIM group, particularly in the biceps brachii (45%) and rectus femoris (40%). Moreover, fibrillation was significantly more prevalent in the IIM group compared to the pathological control group. Finally, a strong correlation was observed between reduced MUP duration and the severity of muscle fiber atrophy and necrosis.

Multi-MUP qEMG provides objective, quantifiable data that correlates strongly with histopathological markers of inflammation and fiber damage. Although it does not replace biopsy for definitive subtyping, qEMG significantly enhances the diagnostic reliability and neurophysiological assessment of patients with suspected IIM.

BASIC MYOLOGY

Abstract P008 - Cod. 143047

IMMUNE-MEDIATED NECROTIZING MYOPATHY: A RETROSPECTIVE ANALYSIS BETWEEN REAL LIFE DATA AND EXISTING EVIDENCE

Bertasini M.*¹, Vattemi G.N.A.¹, Cassandrini D.A.², Orsolini G.³, Marchetto G.¹, Tonin P.¹

¹ *Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, Verona, Italy,* ² *Immunology Unit, University Hospital, Azienda Ospedaliera Universitaria Integrata, Verona,*

Italy, Verona, Italy, ³ Unit of Rheumatology, Department of Medicine, University of Verona, Verona, Italy

Immune-mediated necrotizing myopathy (IMNM) is a rare inflammatory myopathy characterized by severe proximal muscle weakness, markedly elevated creatine kinase (CK) levels, and a distinctive autoantibody profile. Based on serology, three main subtypes are recognized: anti-HMGCR-positive, anti-SRP-positive, and a seronegative forms whose clinical features are still being investigated.

In this study, we retrospectively analyzed 90 patients diagnosed with IMNM at the Verona referral center, aiming to compare real-life data with existing evidence, with particular attention to double seronegative patients. Clinical manifestations, comorbidities, laboratory findings, autoantibody profiles (anti-SRP, anti-HMGCR, and other myositis specific and associated antibodies), instrumental evaluations (electromyography and muscle MRI), and muscle biopsy features were collected.

Anti-HMGCR positivity was strongly associated with prior statin exposure and older age at disease onset, with predominant proximal muscle weakness and variable CK elevation. Anti-SRP-positive patients exhibited different phenotypes, characterized by frequent dysphagia, and more generalized muscle involvement. Muscle biopsies consistently showed necrotic fibers across all groups, while MHCI expression and membrane attack complex deposition were differently expressed.

Notably, patients negative for anti-SRP and anti-HMGCR antibodies exhibited marked clinical heterogeneity and a higher prevalence of additional autoantibodies, including ANA and other myositis-associated antibodies, suggesting overlapping autoimmune phenotypes. Overall disease severity did not correlate strictly with autoantibody profile, CK value and instrumental data. Unlike previous reports in our patient population a low association with malignancy was found.

BASIC MYOLOGY

Abstract P010 - Cod. 143489

LAMINA-ASSOCIATED SIGNALING PATHWAYS IN SKELETAL MUSCLE

Lattanzi G.*

CNR Institute of Molecular Genetics "Luigi Luca Cavalli-Sforza", Bologna, Italy

The nuclear lamina is an hub for cellular signaling. Mechanosignaling is transduced at the nuclear lamina through the linker of nucleoskeleton and cytoskeleton (LINC) complex and involves several transcription factors and kinases as YAP and ATM. Signals related to cell growth and contractility are targeted through the kinase AKT or the corticoid receptors, which also interact with lamin A/C.

This presentation recapitulates available knowledge on the nuclear lamina as a signal transducer platform and a gatekeeper for stress signals.

The nuclear lamina appears to be an integrating platform between diverse signaling pathways both in health and disease. At least the ATM-driven signals, and YAP modulation by mechanical stimuli affect more than the mechanical response of muscle cells and may play a

role in the activation of pathogenetic pathways when mutations in LMNA or related genes cause muscular laminopathies.

Studies aimed at identifying a unifying model of nuclear lamina - related skeletal muscle signaling network, even based on existing data are needed. The definition of such network could provide relevant targets for therapeutic molecules not only for muscular laminopathies, but possibly also for other muscle diseases.

CONGENITAL MYOPATHIES

Abstract P022 - Cod. 143380

ASYMMETRIC MYOPATHY DUE TO SOMATIC MOSAICISM OF THE DMD GENE IN A MALE PATIENT

Di Marco C.*², Torchia E.², Ravera B.², Marchese D.², Monforte M.², Tiziano F.D.¹, Ricci E.², Bortolani S.²

¹ Istituto di Medicina Genomica, Università Cattolica del Sacro Cuore, Roma, Italy, ² Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia

Asymmetric muscle involvement can be observed across several genetic myopathies, including facioscapulohumeral muscular dystrophy, female carriers of Duchenne/Becker muscular dystrophy, limb-girdle muscular dystrophies (LGMD) type R2 or R12. Possible genetic explanations for marked asymmetry include skewed X-chromosome inactivation in X-linked disorders, heteroplasmy in mitochondrial diseases and somatic mosaicism; however, in other cases, the biological basis of asymmetry remains unclear.

We describe the case of a 35-year-old male presenting with progressive left-sided hemi-atrophy and no family history of neuromuscular disorders.

In 2020, the patient noticed difficulties in climbing stairs and carrying heavy objects using his left limbs, associated with elevated serum creatine kinase levels (1951 IU/L). He reported no dysphagia or dyspnea. Electromyography revealed a bilateral myopathic pattern. Muscle MRI demonstrated asymmetric involvement, with predominant left-sided fatty replacement of hip flexor, hip extensor, thigh adductor and knee extensor muscles, as well as bilateral but asymmetric involvement of posterior thigh and plantar flexor muscles. A muscle biopsy, performed in the left vastus lateralis, showed dystrophic changes with increased fiber size variability and necrotic fibers; immunohistochemistry revealed a mosaic of dystrophin-positive and negative myofibers, around 15% dystrophin negative fibers. Genetic testing identified a somatic mosaicism for a DMD gene mutation, c.8357G > A p.(Trp2786Ter), detected in approximately 76% of cells. Karyotyping revealed a normal male XY asset. Cardiac evaluation did not reveal any clinically relevant abnormalities.

Somatic mosaicism of the DMD gene can rarely account for a predominant asymmetric myopathy in male patients, therefore should be considered in the differential diagnosis of asymmetric muscle involvement.

CONGENITAL MYOPATHIES

Abstract P024 - Cod. 143448

CLINICAL AND HISTOPATHOLOGICAL INSIGHTS FROM A NOVEL CASE OF PLEC-RELATED MYOPATHY

Iannaccone D.^{*1}, Marco A.¹, Gianfredi A.³, Baratto S.⁴, Nigro S.¹, Traverso M.⁵, Panicucci C.⁴, Trucco F.², Bruno C.⁴, Fiorillo C.²

¹ Pediatric Neurology and Muscle Disease Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy., Genova, Italy, ² University of Genoa and IRCCS Istituto Giannina Gaslini, Genova, Italy., Genova, Italy, ³ Neuroscience Department, Meyer Children's Hospital IRCCS, Florence, Italy., Firenze, Italy, ⁴ Centre of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genoa, Italy., Genova, Italy, ⁵ UOC Genetica Medica, IRCCS Istituto Giannina Gaslini, Genoa, Italy., Genova, Italy

Plectin, encoded by PLEC gene, is a cytolinker protein playing a crucial role in tissue stability. Mutations in PLEC cause plectinopathies, most commonly epidermolysis bullosa simplex with muscular dystrophy, but additional muscular phenotypes with myasthenic features are described.

We describe a child carrying two novel heterozygous PLEC variants of uncertain significance, presenting with ophthalmoparesis and muscle weakness without skin involvement. The diagnostic work-up included detailed clinical evaluation, muscle MRI and the myopathological study.

The patient presented at age of 3 years for motor clumsiness, with difficulty climbing and descending stairs and persistently elevated CPK (> 1000 U/L). Brain and spinal MRI and cardiac evaluation were normal. No cutaneous manifestations were observed. ENG was normal; EMG showed polyphasic motor unit potentials. Repetitive nerve stimulation demonstrated a significant decrement consistent with neuromuscular junction dysfunction, and pyridostigmine resulted in partial benefit.

At 9 years of age, the patient showed myopathic facies with ptosis, ophthalmoparesis, diffuse hypotonia, distal laxity, and muscle weakness, associated with scapular winging, chest wall deformity, scoliosis, waddling gait, and positive Gowers' sign. Gene panel analysis identified variants in PLEC one maternal c.3382C > T (p.Q1128X), likely pathogenic and paternal c.8393C > T (p.T2798M) likely benign. Muscle biopsy revealed marked myopathic changes with prominent myofibrillar abnormalities and reduced COX activity; PLEC immunostaining was performed. Muscle MRI showed bilateral symmetrical fatty infiltration of gluteal, posterior thigh, and calf muscles, predominantly involving tibialis anterior, soleus, and peroneal muscles.

This case expands the phenotypic spectrum of plectin-related myopathies and highlights distinctive biopsy and MRI findings useful for diagnosis.

CONGENITAL MYOPATHIES

Abstract P026 - Cod. 143288

EARLY ONSET ACTA1-RELATED FACIO-SCAPULOOPERONEAL CONGENITAL MYOPATHY (CMYO): CHARACTERIZATION OF TWO CHILDREN

Giannotta M.^{*7}, Trentin F.⁷, Scarpini G.⁷, Palombo F.², Maffei M.⁹, Valentino M.L.³, Pastorelli F.⁸, Ramacieri G.⁵, Das B.⁴, Cordelli

D.M.⁵, Malfatti E.⁶, Pini A.¹

¹ UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS ISNB Istituto delle Scienze Neurologiche di Bologna, Ospedale Bellaria, Bologna, Italy, ² Programma di Neurogenetica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ³ Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy, ⁴ Mondor Institute of Biomedical Research, University of Paris-Est Créteil, INSERM U955, 8 rue du Général Sarraill, 94010, Créteil, France, ⁵ Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università di Bologna, Bologna, Italy, ⁶ AP-HP, Reference Center for Neuromuscular Diseases, Henri Mondor Hospital, 1 Rue Gustave Eiffel, 94010, Créteil, France, ⁷ UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna Ospedale Bellaria, Bologna, Italy, ⁸ UOC Neurologia, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ⁹ Programma di Neuroradiologia con Tecniche di elevata complessità, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

The ACTA1 gene (1q42.13) encodes skeletal muscle α -actin. Variants in this gene are associated with a wide spectrum of phenotypes. Among these, the scapuloperoneal phenotype is particularly rare and is characterized by slow progression, scapular winging, wrist extensor weakness, finger and foot drop, mild facial weakness, scoliosis, Achilles tendon contractures, and reduced deep tendon reflexes (Armstrong et al. 1966, Zukosky et al. 2015, Caramizaru et al. NAN accepted). Muscle biopsies typically show myopathic changes, fiber-type disproportion, and more rarely cores and rods (Caramizaru et al. NAN accepted).

We describe two unrelated patients with a facio-scapuloperoneal phenotype, carrying different heterozygous variants in NM_001100.4(ACTA1): patient 1 (P1) harbored the c.275_277del, p.(Phe92del), previously reported in association with a bulbar weakness and developmental delay (Harikrishna, 2024); patient 2 (P2) carried the c.307C > T, p.(His103Tyr) variant, which has not previously been linked to a specific phenotype.

Both patients showed early childhood onset hypomimia, neck flexors and scapular girdle weakness and bilateral foot drop. Electroneuromyography in P1 demonstrated denervation and reinnervation at 6 years of age and, at 23 years, absent right and reduced left peroneal cMAP, and absent F-waves. Muscle MRI revealed fatty replacement predominantly affecting the gluteus medius and minimus and posterior thigh muscles, with relative sparing of the gluteus maximus. Tibialis anterior muscles were severely involved. Muscle biopsies showed fiber-size variability, severely hypotrophic fibers and nuclear internalizations.

We reported two early-onset cases of a rare ACTA1-related facio-scapuloperoneal phenotype, carrying one novel and one already reported ACTA1 pathogenic variant thus expanding the genotype ACTA1-related CMYO.

CONGENITAL MYOPATHIES

Abstract P028 - Cod. 142974

EXPANDING THE PHENOTYPIC SPECTRUM OF ADGRG6 MUTATIONS: A CASE REPORT

Catteruccia M.^{*1}, Fattori F.², Tosi M.¹, Verardo M.¹, Diodato D.¹,

Bertini E.¹, D'Amico A.¹

¹ Unit of Muscular and Neurodegenerative Disorders, Bambino Gesù Children's Research Hospital, Rome, Italy, ² Translational Cytogenomics Research Unit RCCS, Bambino Gesù Children's Hospital, Rome, Italy

The adhesion G protein-coupled receptor (aGPCR) GPR126/ADGRG6 plays an important role in several physiological functions, such as embryonic development, myelination and peripheral nerve repair. Pathogenic variants in ADGRG6 have been associated with Lethal congenital contracture syndrome-9 (LCCS9), an autosomal recessive disorder characterized by multiple flexion and extension contractures resulting from reduced or absent fetal movement.

To better define the clinical phenotype associated with ADGRG6 mutations

We report the case of an 14-year-old patient presenting at birth with low weight, generalized hypotonia, respiratory distress requiring intubation, difficulty in suctioning and swallowing requesting nasogastric feeding, distal arthrogryposis, facial dysmorphic features, laryngomalacia, absent osteotendinous reflexes. Tracheostomy and gastrostomy were subsequently performed. Creatinases levels were normal. EMG data were consistent with signs of chronic peripheral neurogenic injury, with normal sensitive electroneurography and repetitive stimulation studies. Muscle biopsy showed aspects of subacute neurogenic damage.

WES analysis showed compound heterozygous missense variants in ADGRG6 segregating from parents.

Clinical condition have improved over time and the baby progressively achieved all motor milestones, she was weaned from mechanical ventilation, facial bilateral ptosis became evident, a marked dysphagia persists thus she is still exclusively gastrostomy-fed.

This case expands the phenotypic spectrum associated with ADGRG6 mutations describing a long term follow-up and helps to clarify possible genotype-phenotype correlation. Indeed while homozygous nonsense mutation are reported in association to severe phenotype, missense heterozygous variants may result in mild and better evolving clinical manifestations.

CONGENITAL MYOPATHIES

Abstract P030 - Cod. 143356

STORMORKEN SYNDROME AND TUBULAR AGGREGATE MYOPATHY CAUSED BY PATHOGENIC VARIANTS IN STIM1: TWO SIDES OF THE SAME COIN

Palombo F.^{*1}, Valentino M.L.¹, Giannotta M.³, Maffei M.², Das B.⁴, Piardi F.⁵, Trentin F.³, Vitale I.¹¹, Scarpini G.³, De Gaetano L.⁶, Cordelli D.M.⁷, Cantalupo G.⁸, Malfatti E.⁹, Carelli V.¹⁰, Pini A.³

¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neurogenetica, Bologna, Italy, ² IRCCS Istituto delle Scienze Neurologiche di Bologna, Programma di Neuroradiologia con Tecniche di elevata complessità, Bologna, Italy, ³ IRCCS Istituto delle Scienze Neurologiche di Bologna, UOS Malattie Neuromuscolari dell'Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, Bologna, Italy, ⁴ Mondor Institute of Biomedical Research, University of Paris-Est Créteil, INSERM U955, 8 rue du Général Sarrail, Créteil, France, ⁵ IRCCS Sacro Cuore Don Calabria, Negrar, Italy, ⁶ Department of Innovation Medicine and

Engineering, University of Verona, Verona, Italy, ⁷ IRCCS Istituto delle Scienze Neurologiche di Bologna, UO Neuropsichiatria dell'Età Pediatrica, Bologna, Italy, ⁸ Child Neuropsychiatry Unit, Department of Children and Maternal Health, AOUI Verona, Verona, Italy, ⁹ AP-HP, Reference Center for Neuromuscular Diseases, Henri Mondor Hospital, 1 Rue Gustave Eiffel, Créteil, France, ¹⁰ Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy, ¹¹ Department of Medical Science-Pediatrics, University of Ferrara, Ferrara, Italy

Stromal interaction molecule 1 (STIM1) is a reticular Ca²⁺ sensor conveying the endoplasmic reticulum calcium load to store-operated channels at the plasma membrane. Dominant gain-of-function pathogenic variants in STIM1 induce excessive extracellular Ca²⁺ entry causing tubular aggregate myopathy (TAM) and Stormorken syndrome (STRMK). TAM and STRMK are spectra of the same multisystem disease characterized by muscle weakness, miosis, thrombocytopenia, hyposplenism and short stature.

We report two STIM1 patients

Patient 1, a 17-year-old girl with a cardiopathy diagnosed at 7 months of pregnancy, corrected by surgery at birth. She complained fatigue, attributed to her heart condition, and limb weakness. At 4 years elevated CK levels (439 U/L) were found. In 2022 hyperCKemia (1215 U/L), elevated GOT, GPT, thrombocytopenia, hypocalcemia, hyposplenism and hypothyroidism were detected. CK values were consistently > 554 U/L. Muscle MRI documented widespread fatty infiltration of pelvis muscles whereas gracilis and semitendinosus were less affected. Muscle biopsy showed the presence of TAM. Electron microscopy confirmed STIM1 hallmarks. Patient 2 is 7-year-old boy with a Developmental Coordination Disorder diagnosis. Since 5 years elevated CK levels (580-1461 U/L) were found, associated with minimal proximal pelvic weakness. Blood test and abdominal ultrasound were normal. Muscle MRI is scheduled

Trio-WES analysis identified a de novo pathogenic variant in STIM1 in both patients: c.343A > T;p.(Ile115Phe) in P1 and c.326A > G;p.(His109Arg) in P2. Variants were reported in literature and for the c.343A > T there is a strong correlation with the phenotypes reported while it is possible that P2 is too young to show all the clinical signs of STRMK

CONGENITAL MYOPATHIES

Abstract P032 - Cod. 143499

WHEN DOUBLE TROUBLES COMPLICATE A DIAGNOSIS: ANKYLOSING SPONDYLITIS IN A PATIENT WITH CONGENITAL MYOPATHY

Maccarrone G.^{*}, Gadaleta G., Urbano G., Vercelli L., Mongini T.E. Neuromuscular Unit, Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy

Rheumatological and neuromuscular disorders may share clinical features, resulting in complex clinical presentations.

To describe an atypical neuromuscular case with a concomitant rheumatological disease and to emphasize red flags and atypical signs that should prevent diagnostic narrowing.

We present an 18-year-old male with Asperger syndrome who, since the age of 6 years, has presented with leg myalgias, recurrent

falls, bilateral hip pain followed since the age of 10 years by spinal stiffness, hyperlordosis, scoliosis, and distal joint hyperlaxity, with a slowly progressive course.

Creatine kinase levels, lactic acid, electromyography, and metabolic and immune–rheumatological screening were normal.

Within the diagnostic work-up, thigh MRI demonstrated marked bilateral muscular atrophy consistent with a myopathic process, but also marked inflammatory joint changes involving both knees and hips. Muscle hypotrophy, ligamentous laxity, and axial involvement raised suspicion of a congenital myopathy, confirmed with a genetic next-generation sequencing panel for myopathies identifying a likely pathogenic heterozygous COL6A3 variant (c.3071-2A > G), together with a heterozygous ADGRL1 variant of uncertain significance (c.551C > T), potentially related to the neurodevelopmental condition.

In this context, clinically relevant arthritis and a subsequent pelvic X-ray showing sacroiliitis prompted rheumatological referral, leading to the diagnosis of HLA-B27–negative ankylosing spondylitis, with marked improvement in pain and stiffness after adalimumab treatment.

In atypical neuromuscular presentations, coexisting conditions should not be overlooked, particularly when a treatable disorder is involved. Accordingly, signs of remarkable juvenile arthritis inconsistent with a pure myopathy represent key red flags. Therefore, multidisciplinary evaluations concurrent with genetic testing are essential to avoid diagnostic delay and missed therapeutic opportunities.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P034 - Cod. 143451

A SIMPLIFIED GIVINOSTAT DOSING REGIMEN MINIMIZES EXPOSURE DIFFERENCES AND DOSE REDUCTIONS IN HIGHER-WEIGHT PATIENTS

Mercuri E.M.^{*1}, Bellanti F.², Cazzaniga S.³, Bettica P.³, McDonald C.M.⁴

¹ Pediatric Neurology Institute, Catholic University, Rome, Italy, ² Certara, Princeton, New Jersey, United States of America, ³ Italfarmaco S.p.A., Milan, Italy, ⁴ Neuromuscular Research Center, Department of Physical Medicine and Rehabilitation, University of California Davis, Sacramento, California, United States of America

Givinostat is an oral histone deacetylase inhibitor indicated for Duchenne muscular dystrophy in patients aged ≥6 years. In the phase 3 EPIDYS study, a weight-based starting dose and flexible treatment regimen allowed dose adjustments for low platelet levels. Higher givinostat exposures initially occurred in heavier patients, but dose reductions led to similar exposures.

To evaluate a simplified regimen that reduced the number of weight-based dosing groups from 9 to 4 and modified doses for higher-weight patients.

Simulated givinostat exposures were comparable in the 10–20 kg and 20–40 kg groups (area under the curve (AUC)₀₋₁₂: 385 and 434 hr•ng/mL) but slightly higher in the 40–60 kg and > 60 kg groups (AUC₀₋₁₂ 504 and 536 hr•ng/mL) following the first admin-

istration. At steady state, following final dose modifications, simulated exposures were comparable across body weights (AUC_{0-tau}: 367, 377, 404, and 417 hr•ng/mL for 10–20 kg, 20–40 kg, 40–60 kg, and > 60 kg groups, respectively). Dose reduction was required in 41.5% of virtual patients; most occurred within the first 3 months.

The revised regimen ensures consistent exposures across weight groups while simplifying dosing and lowering the risk of thrombocytopenia-related reductions. This aligns with EPIDYS, wherein > 95% of patients completed the study without clinical manifestations after dose reductions to manage platelet decreases.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P036 - Cod. 143450

CARDIAC SAFETY DATA FOR GIVINOSTAT IN AMBULANT PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY: RESULTS FROM THE EPIDYS STUDY

Mercuri E.M.^{*1}, Byrne B.J.², Niks E.H.³, Schara--Schmidt U.⁴, Willis T.⁵, Le Tourneau T.⁶, Boespflug--Tanguy O.⁷, Guglieri M.⁸, Muelas N.⁹, Andrés D.G.¹⁰, Phan H.C.¹¹, Díaz S.C.¹², Bourke J.⁸, Cazzaniga S.¹³

¹ Pediatric Neurology Institute, Catholic University, Rome, Italy, ² Child Health Research Institute, Department of Pediatrics, University of Florida, Gainesville, FL, United States of America, ³ Department of Neurology, Leiden University Medical Center, Leiden, Netherlands, ⁴ Department of Pediatric Neurology, Center of Neuromuscular Disorders in Children and Adolescents, Children's University Hospital Essen, University of Duisburg-Essen, Essen, Germany, ⁵ The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry, United Kingdom, ⁶ Institute Of Thorax, University Nantes, Nantes, France, ⁷ APHP and Université Paris Cité, Paris, France, ⁸ The John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, ⁹ Neuromuscular Diseases Unit, Neurology Department, Hospital Universitari I Politécnic La Fe, Valencia, Spain, ¹⁰ Hospital Universitario Vall De Hebron, Barcelona, Spain, ¹¹ MD Rare Disease Research, LLC, Atlanta, Georgia, United States of America, ¹² Pediatric Arrhythmias, Inherited Cardiac Diseases and Sudden Death Unit, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain, ¹³ Italfarmaco S.p.A., Milan, Italy

Givinostat, a histone deacetylase (HDAC) inhibitor, is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients aged ≥6 years based on results from the multicenter, randomized, double-blind, placebo-controlled, phase 3 EPIDYS trial. DMD is associated with dilated cardiomyopathy, and electrocardiogram (ECG) changes have been observed in clinical trials of other HDAC inhibitors.

To evaluate the safety of givinostat on cardiac function assessed by ECG and echocardiogram (ECHO) parameters from patients in the EPIDYS trial.

The mean (standard deviation [SD]) Fridericia-corrected QT interval (QTcF) change from baseline (CFB) at end of study (EOS) was –6.4 (16.87) ms and –1.3 ms (12.83) for the givinostat and placebo groups, respectively; no QTcF prolongation of > 450 ms was recorded. A QTcF CFB of > 30 ms and < 60 ms was observed in 10 (5.6%) patients in the givinostat group; no patients had a CFB of > 60 ms

at any visit. Other ECG parameters remained stable throughout the study. The mean (SD) left ventricular ejection fraction (ECHO-LVEF) CFB at EOS had a numerically smaller trend with givinostat treatment (-1.2 [6.81]) versus placebo (-3.4 [7.57]).

No QTc prolongation was recorded with givinostat or placebo, and other ECG parameters remained stable. A beneficial trend change in LVEF from baseline to EOS was observed, suggesting that givinostat helped preserve LV-function versus placebo.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P038 - Cod. 143508

CARRIERS OF DMD GENE VARIANTS: AN INTERNATIONAL SURVEY TO IDENTIFY GAPS IN CARE

Pietro R.^{*1}, Behar L.¹, Houwen S.², Bourke J.¹, Meijer--Krom Y.³, Ferlini A.⁴, Robinson C.¹, Wong K.¹, Geagan C.¹, Muni--Lofra R.¹, Segovia S.¹, Fortunato F.⁴, Reuben E.⁵, Franken M.⁶, Zito I.⁷, Voermans N.⁸, Sarkozy A.⁹, Guglieri M.¹

¹ John Walton Muscular Dystrophy Research Centre, Newcastle University, United Kingdom, ² Dept Rehabilitation, Amalia Childrens' Hospital, Radboud Univ Med Center & Duchenne Center, Nijmegen, Netherlands, ³ Dept Neurology, Leiden Univ Med Center & Duchenne Centre, Leiden, Netherlands, ⁴ Medical Genetics Unit, Dept Medical Science, Univ Ferrara, Ferrara, Italy, ⁵ Duchenne UK, London, United Kingdom, ⁶ Duchenne Parent Project, Amsterdam, Netherlands, ⁷ Parent Project, Rome, Italy, ⁸ Dept Neurology, Donders Inst for Brain, Cognition and Behaviour, Radboud Univ Med Center, Nijmegen, Netherlands, ⁹ Dubowitz Neuromuscular Centre, Gt Ormond St Hosp for Children, London, United Kingdom

Female carriers of DMD gene variants may develop skeletal, cardiac, and neuropsychological manifestations; however, the prevalence and clinical spectrum of these features remain incompletely characterised. Limited evidence hampers the development of optimal surveillance strategies and clinical management for this population.

We created an international survey of carriers of Duchenne (DMD) and Becker (BMD) muscular dystrophy across the United Kingdom, the Netherlands, and Italy, in collaboration with patient organisations. The survey was also open to carers of individuals living with DMD or BMD who were not carriers. Anonymised data were collected on neuromuscular, cardiac, and neuropsychological symptoms, diagnostic pathways, and healthcare provision.

A total of 446 women responded to the survey; 382 were carriers and 64 were carers but not carriers. Overall, 78.5% of carriers reported at least one muscle symptom, most commonly fatigue (63.9%) and muscle pain (58.5%), with no significant difference between DMD and BMD carriers ($p = 0.74$). Only 2.1% of carriers reported wheelchair use. Cardiac involvement was reported by 22.4% of carriers, yet only half of these received cardioprotective treatment; 11.1% had never undergone cardiac evaluation. Neuropsychological comorbidities were common in carriers, particularly anxiety (34.6%) and depression (28.7%). Muscle manifestations were significantly more frequent in carriers, irrespective of caregiving status, than in carers who were not carriers.

Female carriers of DMD gene variants frequently report multisystem involvement but remain insufficiently recognised in clinical practice.

These findings highlight gaps in care and support the need for improved surveillance approaches.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P040 - Cod. 143480

EFFICACY AND SAFETY OF SEMAGLUTIDE IN TWO OBESE PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY (DMD)

Mela F.¹, Pedemonte M.^{*2}, Tantari G.³, Brolatti N.⁴, Trucco F.², Amata F.¹, Latinakis G.⁴, Morando S.⁴, Angelelli A.³, Di Iorgi N.³, D'Annunzio G.³, Maghnie M.³, Bruno C.⁴, Panicucci C.⁴

¹ Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, DiNOGMI, University of Genova, Genova, Italy, ² Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy, ³ Department of Pediatrics, IRCCS Istituto Giannina Gaslini, Genova, Italy, ⁴ Centre of Translational and Experimental Myology, IRCCS Istituto Giannina Gaslini, Genova, Italy

DMD patients have a high prevalence of obesity and metabolic syndrome, often exceeding 50% in adolescence, largely due to long-term glucocorticoid therapy and reduced physical activity. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as semaglutide, are effective drugs approved for obesity treatment and recommended for individuals > 12 years with a body mass index (BMI) > 95th percentile or adults with BMI > 30 kg/m². Currently, no data are available in literature on the use of this drug for obese DMD patients.

To evaluate the efficacy and safety of semaglutide therapy in two obese DMD patients.

Two non-ambulant DMD patients with BMI > 30 kg/m² or > 95th percentile, received subcutaneous semaglutide weekly. Anthropometric and metabolic parameters were collected at baseline (T0) and after three (T1), six (T2), and twelve months (T3) after treatment initiation; bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA) were performed at T0 and T3. At T0, a low-calorie diet was recommended. Patient 1 (26 years) and Patient 2 (14 years) were followed for 12 and 6 months, respectively. BMI decreased by 21% at T3 in Patient 1 and by 7% at T2 in Patient 2. Both patients showed altered fasting glucose at T0, normalized at T1. In Patient 1, DXA and BIA documented an 11% fat-mass reduction at T3, with preservation of fat-free mass.

Semaglutide was well tolerated, without gastrointestinal adverse reactions requiring treatment discontinuation.

These preliminary findings suggests that semaglutide may represent a feasible option for obesity management in DMD. Longer and larger studies are required to confirm efficacy and safety.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P042 - Cod. 143300

FACE-DMD: FACIAL ASPECT AND IMPLICIT COGNITION OF EMOTIONS IN DUCHENNE MUSCULAR DYSTROPHY

Khalil S.^{*1}, Conti C.¹, Pratile D.C.¹, Gardani A.², Parravicini S.¹,

Oldrati V.³, Buchignani B.⁴, Ballante E.⁵, D'Angelo M.G.³, Cristofani P.⁴, Battini R.⁴, Berardinelli A.²

¹ Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy, ² Department of Child Neurology and Psychiatry, IRCCS C. Mondino Foundation, Pavia, Italy, ³ Scientific Institute, IRCCS E. Medea, Bosisio Parini, Italy, ⁴ Department of Neuroscience, IRCCS Stella Maris Foundation, Pisa, Italy, ⁵ Department of Political and Social Sciences, University of Pavia, Pavia, Italy

Duchenne muscular dystrophy (DMD) is a progressive X-linked neuromuscular disease that primarily affects males, caused by mutations in the DMD gene, that impair dystrophin synthesis. In addition to muscle degeneration, DMD patients have heterogeneous neuropsychological profiles, with the risk of presenting cognitive deficits and other neuropsychiatric comorbidities. Recent studies have elucidated the expression profile of dystrophin isoforms in the human central nervous system (CNS), shifting the focus to limbic structures (e.g., amygdala and thalamus) where the protein is most represented. These areas, when damaged, are involved in emotional processing deficits. In this context, assessment of social cognition skills is not part of routine neuropsychological assessments of DMD.

A previous study conducted at the Child Neuropsychiatry Unit of the IRCCS Fondazione Mondino showed a significant deficit in social cognition skills, particularly in the recognition of the affective value of facial expressions, tested with a standardized neuropsychological rating scale. Based on these results, this function was further investigated by studying the possible involvement of extra-geniculostriate pathways using an experimental setup of subliminal emotional priming with backward masking techniques. This study aimed to fill the knowledge gap about social cognition skills in DMD with a specifically designed experimental protocol.

Our preliminary results are presented here and compared with those of HC and other neuromuscular disorders.

These data support the hypothesis of a social cognition deficit in the neuropsychological phenotype of DMD and the need to confirm the preliminary results obtained in order to implement the assessment of these skills in the diagnostic-rehabilitation stages.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P044 - Cod. 143460

GIVINOSTAT REDUCES THE DECLINE OF CONTRACTILE CROSS-SECTIONAL AREA AND DECREASES FAT INFILTRATION IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Vandenborne K.¹, Willcocks R.¹, Bettica P.², Cazzaniga S.², Alessi F.², Mercuri E.M.*³

¹ University of Florida, Gainesville, Florida, United States of America, ² Italfarmaco S.p.A., Milan, Italy, ³ Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy

Givinostat is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulant boys aged ≥6 years. The phase 3 EPIDYS trial was a randomized, double-blind, placebo-controlled study evaluating the safety, tolerability, and ef-

ficacy of givinostat. Contractile cross-sectional area (cCSA) and fat fraction are quantitative measures of DMD disease progression, reflecting the amount of functional muscle tissue available for force generation and the extent of muscle tissue replacement by fat, respectively.

To measure cCSA and fat fraction in patients with a baseline vastus lateralis fat fraction > 5% to ≤30% measured by magnetic resonance spectroscopy from the EPIDYS trial.

At the end of the 18-month EPIDYS trial, the differences in least squares (LS) means (95% CI) between the givinostat and placebo groups for cCSA in the biceps femoris long head, hamstrings, quadriceps, semitendinosus, and vastus lateralis were 0.43 (0.14, 0.73; P = 0.005), 1.02 (0.47, 1.58, P < 0.001), 1.20 (0.16, 2.23; P = 0.023), 0.47 (0.13, 0.80, P = 0.006), and 0.61 (0.04, 1.17, P = 0.035), respectively. Further, differences in LS means for fat fraction in the same muscles were -4.60 (-8.22, -0.99; P = 0.013), -4.00 (-6.59, -1.40; P = 0.003), -4.07 (-6.42, -1.72; P = 0.001), -3.43 (-5.80, -1.06; P = 0.005), and -3.86 (-6.36, -1.35; P = 0.003), respectively. Similar results were observed as early as 48 weeks into the study.

Givinostat treatment appears to be associated with significantly less decline in muscle contractile area and reduced fat infiltration compared with placebo, suggesting attenuation of muscle loss in patients with DMD.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P046 - Cod. 143454

GIVINOSTAT WEIGHT-BASED FLEXIBLE DOSING: RATIONALE AND EFFICACY AT THE DIFFERENT DOSES

Veerapandian A.², Alessi F.³, Cazzaniga S.³, Bettica P.³, Mercuri E.M.*¹

¹ Fondazione Policlinico Gemelli IRCCS, Rome, Italy, ² Department of Pediatrics, Division of Neurology, University of Arkansas for Medical Sciences, Arkansas Children's Hospital, Little Rock, Arkansas, United States of America, ³ Italfarmaco S.p.A., Milan, Italy

Givinostat is a histone deacetylase inhibitor indicated for the treatment of Duchenne muscular dystrophy (DMD). In the phase 3 double-blind, placebo-controlled EPIDYS study, patients with DMD received weight-based givinostat dosing plus standard of care (ie, corticosteroids), starting at dose A or B, depending on study protocol. Doses were adjusted (A to B or B to C) based on predefined rules related to tolerability to achieve the highest tolerated dose for each patient. To evaluate givinostat efficacy based on the final administered dose at week 72 in patients from EPIDYS.

Thirty-nine patients started at dose A, 42 patients started at dose B, and 39 patients received placebo. Dose was reduced in 36 patients. Overall, 21 patients received final dose A, 44 dose B, and 16 dose C. All patients had similar givinostat blood concentrations within the range considered efficacious throughout the study (5 samples/patient). At week 72, the placebo-corrected difference in least squares (LS) mean CFB (95% CI) in 4SC time was A: -2.61 (-4.97, -0.26), B: -1.35 (-3.25, 0.54) and C: -1.90 (-4.48, 0.67). For NSAA, the

LS mean CFB (placebo-corrected) was A: 3.35 (1.07, 5.64), B: 1.24 (−0.57, 3.05), and C: 1.94 (−0.58, 4.46).

Results numerically favored givinostat over placebo across all 3 doses. Flexible dosing enables the highest tolerated givinostat exposure for maximal efficacy while maintaining tolerability. Despite protocol-driven dose reductions, clinical benefit was achieved across all dosing regimens.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P048 - Cod. 143035

MITOCHONDRIAL DNA METHYLATION AND COPY NUMBER: PERIPHERAL AND TISSUE-BASED INDICATORS OF MUSCULAR DYSTROPHIES DISEASE SEVERITY

Dragoni F.^{*1}, Rizzo B.², Dainesi M.I.¹, Di Gerlando R.¹, Minucchi E.¹, Berardinelli A.L.¹, Gagliardi S.¹

¹ IRCCS Mondino Foundation, Pavia, Italy, ² Golgi Cenci Foundation, Abbiategrasso, Italy

Muscular Dystrophies (MD), including Duchenne (DMD) and Becker (BMD) forms, are characterized by progressive muscle wasting driven by DMD gene mutations. Beyond structural defects, mitochondrial dysfunction and impaired ATP production are critical contributors to MD pathogenesis. "Mitoepigenetics", the epigenetic regulation of mitochondrial DNA (mtDNA), represents an emerging field that could clarify the link between genetic mutations and metabolic failure.

This study investigates mtDNA copy number (mtDNA-cn) and D-loop methylation as potential indicators of mitochondrial impairment in MD patients. We analyzed 24 muscle biopsies and 67 blood samples. mtDNA-cn was quantified via RT-qPCR, while DNA methylation levels within the D-loop regulatory region were assessed through high-sensitivity pyrosequencing.

A significant reduction in mtDNA-cn was observed in both muscle biopsies and blood samples of DMD and BMD patients compared to healthy controls ($p < 0.05$), confirming a systemic depletion of mitochondrial density. Interestingly, D-loop methylation profiling revealed a tissue-specific divergence: patients exhibited significantly lower methylation levels in muscle biopsies compared to controls, whereas an opposite, compensatory trend was observed in peripheral blood. Our findings highlight a profound alteration of mitoepigenetic landscape in MD. Reduction of mtDNA-cn underscores the metabolic crisis inherent in dystrophic muscles. Furthermore, the tissue-specific discordance in D-loop methylation suggests that peripheral blood may reflect systemic inflammatory responses, while muscle biopsies capture the primary epigenetic attempt to compensate for mitochondrial decay. These results identify mitoepigenetic signatures as promising indicators of disease severity and provide new insights into the role of mitochondrial DNA regulation in the progression of Duchenne and Becker Dystrophies.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P050 - Cod. 142694

NEUROCOGNITIVE AND EMOTIONAL-BEHAVIORAL PROFILES IN DUCHENNE MUSCULAR DYSTROPHY: A SINGLE-CENTER CLINICAL STUDY IN PEDIATRIC PATIENTS

Sertori F.^{*1}, Re F.¹, D'Alessandro R.¹, Vacchetti M.¹, Arletti L.¹, Campagna A.¹, Mongini T.², Ricci F.¹

¹ Section of Child and Adolescent Neuropsychiatry, Children Hospital "Regina Margherita"-Sant'Anna, University of Turin, Turin, Italy,

² Department of Neurosciences RLM, Neuromuscular Unit, University of Turin, Turin, Italy

Duchenne muscular dystrophy (DMD) is an X-linked disorder caused by mutations in the DMD gene, leading to dystrophin deficiency and progressive muscle degeneration. Increasing evidence links DMD to cognitive impairment and emotional-behavioral difficulties, possibly related to altered expression of brain dystrophin isoforms (Dp71, Dp140, Dp427c).

This study describes the neurocognitive and emotional-behavioral profile of pediatric DMD patients and explores genotype-phenotype associations. We conducted a single-center, cross-sectional observational study on 21 children with genetically confirmed DMD. Clinical and demographic data were collected. Parents completed standardized questionnaires, and structured clinical interviews were administered.

The prevalence of ASD, ADHD, and OCD didn't differ from the general population. However, 35% of patients showed isolated attention deficits, and approximately 80% presented anxiety and depressive symptoms. About genotype-phenotype correlations, autistic traits were more frequent in the Dp140-/Dp71+ group, supporting a possible vulnerability linked to Dp140 absence. Executive functions were largely normative, but 35.3% showed emotional regulation impairments, significantly associated ($p = 0.029$) with multiple clinical items on Conners. Cognitive profiles were heterogeneous: 45.5% had $IQ < 85$ and a significant association ($p = 0.048$) emerged between the Dp140-/Dp71+ genotype and lower cognitive level, suggesting a protective role of Dp140. Language delay (52.4%) correlated with lower IQ, suggesting early cognitive vulnerability.

Children with DMD present heterogeneous neurocognitive and emotional-behavioral profiles, with frequent emotional dysregulation and cognitive vulnerability linked to specific dystrophin isoforms. Early standardized screening is to enable early detection of neuropsychiatric risks and personalized interventions, improving quality of life and social participation.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P052 - Cod. 143442

OPEN-LABEL EXTENSION ANALYSIS SHOWS POTENTIAL DELAY IN AGE AT LOSS OF AMBULATION IN PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY TREATED WITH GIVINOSTAT

David Gómez A.¹, Sansone V.², Parodi A.³, Boespflug--Tanguy O.⁴, Goedecker N.⁵, Bettica P.³, Willis T.⁶, Mercuri E.M.^{*7}

¹ Hospital Universitario Vall De Hebron, Barcelona, Spain, ² The NeMO

Clinical Center in Milan, Neurorehabilitation Unit, Milan, Italy, ³ Italfarmaco S.p.A., Milan, Italy, ⁴ APHP and Université Paris Cité, Paris, France, ⁵ Washington University, St. Louis, Missouri, United States of America, ⁶ The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry, United Kingdom, ⁷ Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy

Givinostat is an oral histone deacetylase inhibitor that was investigated in the phase 3, randomized, double-blind, placebo-controlled EPIDYS trial (NCT02851797). In the 2021 interim analysis of an ongoing, single-arm, open-label extension (OLE) study of the long-term safety, tolerability, and efficacy of givinostat (NCT03373968), givinostat-treated patients showed a delay in median age at persistent loss of ambulation (LoA; ie, permanent inability to walk independently) compared with a matched, natural history corticosteroid-treated external control group.

To evaluate the effect of longer-term givinostat treatment, in combination with standard-of-care corticosteroids, on LoA in patients with DMD aged ≥ 6 years using data through the 2023 cutoff, which provided a larger patient population and an additional 2 years of follow-up since the previous interim analysis.

Among the 225 patients analyzed, 78 experienced persistent LoA. The median (95% CI) age at persistent LoA was 17.3 (15.5-18.1) years.

This updated interim analysis evaluated LoA in patients with DMD with 2 additional years of data from the OLE. These updated OLE data suggest that givinostat consistently delays the onset of LoA in patients with DMD. Relative to published estimates from a meta-analysis reporting a median age at LoA of 11.0-13.4 years in patients treated with corticosteroids alone, the median age at persistent LoA with givinostat was 17.3 years, suggesting a delay in the loss of ambulation in patients treated with givinostat.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P054 - Cod. 143389

PROPOSAL TO IDENTIFY THE FUNCTIONAL PROFILE OF PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY AT DIFFERENT STAGES OF THE DISEASE

Guardani A.^{*1}, Khalil S.², Conti C.², Pratile D.², Berardinelli A.¹

¹ Fondazione Mondino, Pavia, Italy, ² Università degli Studi di Pavia, Pavia, Italy

Duchenne muscular dystrophy is a rare, progressive, hereditary neuromuscular disease linked to the X chromosome. It is caused by a mutation in the gene that codes for dystrophin, a protein essential for muscle function. In patients with Duchenne muscular dystrophy, progressive muscle weakness first affects the lower limbs, but as the disease progresses, control of the trunk and upper limb function are also gradually compromised. Following the loss of walking ability, motor assessment becomes more complex and requires tools adapted to new clinical needs.

The study aims to integrate a functional assessment scale based on qualitative and quantitative analysis of the movement patterns of

patients with DMD, in addition to the modified functional scales of Vignos and Brooke.

In order to assess its consistency and accuracy, the new assessment scale is correlated with standardised tests.

A secondary objective is to assess whether the use of the new scale allows the definition of the patient's functional profile at various stages of the disease and a classification into different functional groups.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P056 - Cod. 143421

PSYCHOPATHOLOGICAL SYMPTOMS IN PATIENTS WITH DMD MEASURED BY SELF-REPORT AND PARENT-REPORT PSYCHOMETRIC QUESTIONNAIRES AND PSYCHOLOGICAL INTERVIEWS

Lattarulo S.^{*1}, Giannotta M.¹, Trentin F.¹, Scarpini G.¹, Laganà V.², Letizia C.², Cordelli D.M.², Pini A.¹

¹ UOS Malattie Neuromuscolari Età Evolutiva, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle scienze Neurologiche di Bologna, Ospedale Bellaria, Bologna, Italy, ² Dipartimento di Scienze Mediche e Chirurgiche (DIMEC), Università di Bologna, Bologna, Italy

Duchenne muscular dystrophy (DMD) is a genetic X-linked condition that causes progressive muscle weakness, with loss of ambulation 12 years, and a multi-systemic involvement requiring an increased level of dependence on caregivers. This characteristic causes emotional and relational effects, other than physical.

Cognitive and psychopathological disorders, such as ASD, ADHD and OCD (Tizzoni et al., 2025; Ricotti et al., 2015), are well documented in DMD, but they have been predominantly assessed through parent-report measures.

This preliminary single-center study aims to investigate the most recurrent psychopathological indicators in a group of adolescent with DMD, using self-report in addition to parent-report questionnaires, with the purpose of highlighting patient's emotional perspective.

Furthermore, psychological interviews were conducted to explore the emerged issues in greater depth and to value the experience of each individual patient.

17 boys with DMD (5 ambulant and 12 non-ambulant), aged between 10 and 18 years, attending our centre, were included. Structured and validated tools were administered, including: Beck Depression Inventory, Child Behavior Check List, Youth Self Report, Multidimensional Anxiety Scale for Children and Conners scales, both in self-report and parents version.

Preliminary results indicate that the majority of subjects exhibited clinically significant values regarding sociability, internalizing problems and presence of selective mutism during childhood.

Self-report tests and interviews highlighted significant separation anxiety associated with increasing needs of help in self-care and awareness of the disease.

This preliminary report highlights the importance of psychological care in DMD adolescents, to improve relational skills and support self-determination as well as internalizing problems.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P058 - Cod. 142963

REAL-WORLD EVIDENCE ON THE EFFICACY AND SAFETY OF GIVINOSTAT IN CHILDREN WITH DUCHENNE MUSCULAR DYSTROPHY: A MONOCENTRIC EXPERIENCE

Tosi M.^{*1}, D'Aurelio E.², De Luca G.¹, Mizzoni I.¹, Carlesi A.³, Catteruccia M.¹, D'Amico A.¹

¹ Unit of Muscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, ² Systems Medicine Department, University of Rome "Tor Vergata", Rome, Italy, ³ Unit of Neurorehabilitation, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy

Givinostat is a histone deacetylase inhibitor recently approved for ambulant boys with Duchenne muscular dystrophy (DMD) aged ≥ 6 years, independent of the underlying genetic mutation. Preclinical and randomized clinical studies have demonstrated improvements in motor function, together with a slowing of muscle damage progression however, real-world safety and efficacy data remain limited.

This was a prospective study to evaluate the clinical efficacy, safety, and dose adjustment requirements of Givinostat in a pediatric DMD cohort treated in a real-world setting. Motor function was assessed at baseline, 3, 6, 12 months (NSAA, 6MWT, PUL2.0, timed tests). Platelets, triglycerides, QTcB guided dosing.

37 ambulant boys were enrolled. 22 followed ≥ 6 months, six for 12. NSAA scores remained stable over follow-up ($\Delta = 0.14 \pm 4.11$ points). The 6MWT showed a mean increased by $+13.05 \pm 46.45$ m, while PUL scores changed minimally ($\Delta = 0.31 \pm 1.44$). Mean times of four step ascent and descent improved by -0.59 ± 1.61 s and -0.89 ± 1.53 s, respectively. Mild diarrhea and thrombocytopenia occurred in 36% and 45% of patients. A gradual increase in triglycerides levels was observed in most patients, exceeding the 300 mg/dL threshold in only one case. Dose reduction was required in 53.3% of patients; no treatment discontinuations were reported. In a real-world setting, treatment with Givinostat required careful monitoring to manage predictable side effects and guide dose adjustment. Overall, Givinostat was well tolerated, and its efficacy profile was consistent with findings from clinical trials. Larger, longer duration studies are needed to confirm the durability of benefit and to further refine dosing algorithms.

DUCHENNE MUSCULAR DYSTROPHY (DMD)

Abstract P060 - Cod. 143197

SHORT PR INTERVAL AND PR SEGMENT ARE SIMPLE AND EARLY BIOMARKERS TO IDENTIFY DUCHENNE MUSCULAR DYSTROPHIES CARRIERS WHO REQUIRE A CLOSE CARDIAC MONITORING

Palladino A., Scutifero M., Picillo E., Passamano L., Politano L.*
Cardiomyology and Medical Genetics - University of Campania Luigi Vanvitelli, Naples, Italy

DMD and BMD carriers) may develop cardiomyopathy after the age of 40, alongside or independently of muscle damage. Myocardial changes are progressive passing from pre-symptomatic cardiomyopathy to dilated cardiomyopathy. Aim of the study was to identify simple and early biomarkers to monitor myocardial involvement in this patient population.

We retrospectively analyzed the ECGs of 42 DMD, 18 BMD carriers and 30 age-matched control subjects and considered these parameters: heart rate (HR), PR interval (PRi), PR segment (PRs) and QT interval.

The mean age of D-carriers was 43.5 ± 15.2 , that of B-carriers 49.4 ± 18.5 and that of control subjects 49.5 ± 10.1 years, without statistically differences.

HR ranged from 74.6 ± 12.5 b/m' (D-carriers) to 75.7 ± 14.1 b/m' in B-carriers and to 74.0 ± 9.7 b/m' in controls, without statistically differences between and among groups. Similarly, the QT_i was not statistically different in D- and B-carriers compared to controls, nor between D- and B-carriers. On the contrary, PRi was significantly shortened in both B- (0.14 ± 0.02 sec vs 0.15 ± 0.01 sec; $P < 0.01$) and D-carriers (0.13 ± 0.01 sec vs 0.15 ± 0.01 sec; $P < 0.0002$) compared to controls. However, the PRs was found to be a discriminating parameter between D-carriers and B-carriers or controls, as the average value in D-carriers was statistically different compared to B-carriers and controls (0.03 ± 0.01 sec vs 0.05 ± 0.01 sec; $P < 0.0001$).

PRi and PRs are simple and easy biomarkers to identify DMD carriers who require a close cardiac monitoring.

METABOLIC MYOPATHIES

Abstract P172 - Cod. 143079

ACUTE RESPIRATORY FAILURE AS FIRST MANIFESTATION OF LATE ONSET POMPE DISEASE (LOPD) IN TWO PATIENTS: CASE REPORTS AND LITERATURE REVIEW

Auletta M.^{*1}, Di Muzio A.², Sancricca C.³, Guido P.¹, Servidei S.¹

¹ Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italy, ² Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University, Chieti, Italy, ³ Fondazione UILDM Lazio Onlus, Rome, Italy

LOPD is a lysosomal storage disorder typically presenting with progressive limb-girdle muscle weakness and respiratory insufficiency. Severe acute respiratory failure at disease onset in otherwise normal individuals is very rarely reported in the literature.

We describe two LOPD patients presenting with acute hypercapnic respiratory failure at onset in the absence of neuromuscular signs and symptoms.

Case 1: A 31-year-old healthy woman developed acute hypercapnic respiratory failure and coma needing intensive care unit (ICU) admission and tracheostomy. Later, she developed proximal muscle weakness. Muscle MRI and biopsy were suggestive of myositis. Immunosuppressive therapy lead to benefits on motor function while she still needed nocturnal non-invasive ventilation. Muscle biochemistry revealed reduced acid maltase levels (17%). Genetic testing

confirmed the LOPD diagnosis showing two pathogenic GAA variants (c.32-13T > G; c.2530_2541del12). Enzyme replacement therapy (ERT) was started leading to respiratory stabilization.

Case 2: A 48-year-old woman with an upper-limb-demanding occupation and a 20-year long history of elevated CK levels with negative muscle biopsy acutely developed hypercapnic respiratory failure. She was admitted to ICU admission and non-invasive ventilation was started. Muscle biochemistry revealed a severe reduction of acid maltase activity (1%). Genetic testing disclosed two GAA heterozygous variants (c.-32-13T > G; del-G2219-2220). ERT was started leading to suspension of non-invasive ventilation use.

These cases remark that LOPD may still represent a diagnostic challenge especially when respiratory involvement is the only clinical manifestation. It is crucial to consider LOPD in the differential diagnosis of acute-onset hypercapnic respiratory failure to allow timely treatment, as ERT can improve respiratory function.

METABOLIC MYOPATHIES

Abstract P174 - Cod. 143511

EXPANDING THE CLINICAL SPECTRUM OF DANON DISEASE: A CASE OF LATE-ONSET VACUOLAR MYOPATHY WITH MILD CARDIAC INVOLVEMENT

Loprieno S.^{*1}, Torri F.¹, Ali" G.², Cenacchi G.³, Torella A.⁴, Nigro V.⁴, Sicilliano G.¹, Ricci G.¹

¹ Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy., Pisa, Italy, ² Pathological Anatomy Unit, Department of Surgical, Medical and Molecular Pathology and Critical Care, University of Pisa, Pisa, Italy., Pisa, Italy, ³ Department of Biomedical and Neuromotor Sciences, University of Bologna, Via Massarenti 9, Bologna 40126, Italy., Bologna, Italy, ⁴ Telethon Institute of Genetics and Medicine (TIGEM), Pozzuoli, Naples, Italy; Department of Precision Medicine, University of Campania "Luigi Vanvitelli," Naples, Italy., Napoli, Italy

Danon disease (DD) is an X-linked dominant vacuolar cardiomyopathy and skeletal myopathy caused by a primary deficiency of lysosome-associated membrane protein-2 (LAMP-2). Male patients typically present with a triad of cardiomyopathy, myopathy, and intellectual disability; the disease course is severe, often leading to death or heart transplantation by the mid-twenties. However, cases of male patients over 50 years of age with mutations in exon 9B and mild clinical symptoms have been reported.

To report a rare case of late-onset Danon disease in a 64-year-old male presenting with a mild phenotype and isolated skeletal myopathy, contrasting with the typical severe course of the disease.

His medical history was remarkable only for bipolar disorder. Cardiac evaluation revealed only mild left ventricular hypertrophy. There was no family history of neuromuscular disease. Neurological evaluation showed both proximal and distal weakness, prominent in the lower limbs.

Diagnostic investigations included electromyography (EMG), which revealed a myopathic pattern in all tested muscles and signs of chronic denervation in the tibialis anterior, normal nerve conduction

studies and serial MRI of the lower limbs which showed bilateral fatty infiltration of the gastrocnemius muscles. Muscle biopsy of the vastus medialis showed intracytoplasmic and subsarcolemmal vacuoles. Electron microscopy confirmed a vacuolar myopathy with scattered areas of myofibrillar disorganization. Genetic testing for vacuolar and metabolic myopathies, mitochondrial disorders, dystrophinopathies, and channelopathies was unremarkable.

Upon re-evaluation, considering the biopsy findings, whole-exome sequencing (WES) was requested. The results revealed a likely pathogenic variant in LAMP-2 (c.1140del, exon 9) on the X chromosome. This finding correlates with the patient's clinical presentation and suggests a milder phenotype associated with this specific variant.

METABOLIC MYOPATHIES

Abstract P176 - Cod. 142684

GENETIC EPIDEMIOLOGY OF NEUTRAL LIPID STORAGE DISORDERS (NLSD)

Angelini C.^{*2}, Missaglia S.¹, Tavian D.¹

¹ Catholic University, Milano, Italy, ² University of Padova, Padova, Italy

There are two types of NLSD: Chanarin Dorfman syndrome (CDS) and Neutral Lipid Storage with myopathy (NLSDM). The cytoplasm of granulocytes in NLSD patients shows the 'Jordans' anomaly' on peripheral blood smear. In CDS, muscle abnormalities affect 40% of subjects. CDS is due to molecular defects in the ABHD5 gene, which encodes an activator of the ATGL lipase that can hydrolyse triacylglycerol in the absence of the ABHD5 protein.

NLSD-M has a myopathic presentation with proximal-distal weakness. In NLSD-M patients, LD accumulation is due to defective ATGL activity, which catalyzes the hydrolysis of fatty acids from triglycerides.

Describe the world epidemiology of genetically proven cases of CDS and NLSDM.

176 CDS and 142 NLSDM cases were identified as of Mediterranean/Middle Eastern origin. We found in Mediterranean countries, 124 CDS cases: 10 in Italy, 3 in Greece, and 48 in Turkey. Two siblings had CNS involvement, myopathy, neurosensory hearing loss, cataracts, nystagmus, strabismus, and mental impairment; molecular analysis revealed the N209* mutation.

Patients with ichthyosis are referred for CK elevation and muscle lipid storage. In Palestine, 5 cases were detected (common mutation c.960+5G > A), 9 in Israel, 4 in Algeria, 26 in Tunisia, 3 in France, 7 in Spain, 4 in Egypt, and 3 in Morocco. 176 CDS patients have been reported worldwide. In India, 19 mutations were found. NLSDI patients have an onset in the first/second decade. Usually, children have congenital ichthyosis, Jordan's anomaly, and liver steatosis; CNS changes are then detected.

CDS is a Mediterranean trait, with different organ involvement from NLSDM in skeletal muscle and skin, revealed with Jordan's anomaly.

METABOLIC MYOPATHIES

Abstract P178 - Cod. 142767

GYG1: MUTATIONS AND CLINICAL PRESENTATION IN THREE PATIENTS

Cassandrini D.A.^{*1}, Bertasini M.², Marchetto G.², Vattemi G.², Santorelli F.³, Tonin P.²

¹ Immunology Unit, University Hospital, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, ² Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, ³ Molecular Medicine for Neurodegenerative and Neuromuscular Diseases Unit, IRCCS Stella Maris Foundation, Pisa, Italy

Polyglucosan body myopathy type 2 (PGBM-2) is caused by a deficiency of glycogenin-1, the enzyme involved in the first step of glycogen synthesis. The pathological hallmark is the presence of polyglucosan bodies which are characterized by abnormally structured glycogen. Autosomal recessive PGBM2 usually manifests in adulthood with slowly progressive weakness involving mostly proximal limb muscles also with an asymmetric presentation.

We report on three patients with GYG1 mutation and different clinical and pathological phenotype. The first, a 80 year-old woman had proximal asymmetric muscle weakness prevalent at upper limbs, the second is a 55 year-old woman with proximal lower limbs muscle weakness and the third patient is a 60 year-old man with distal lower limb weakness. CK was mildly elevated in the third patient. EMG recorded myopathic signs in all the patients. None was affected with cardiomyopathy. Muscle biopsy from the female patients showed a polyglucosan body myopathy while the muscle biopsy from the male patient showed a myopathy with rimmed vacuoles.

Both old- and next-generation sequencing were used to identify the mutations. The first patient had a homozygous splicing mutation c.143+3G > C, the second patients had the homozygous c.304G > C variant while the third patient had a novel homozygous stop mutation c.522G > A (p.Trp174*).

The heterogeneous clinical presentation of our patients confirms the already reported different muscle involvement which may occur in PGBM-2. As far as we know, a myopathy with rimmed vacuoles has never been associated with mutations in GYG1 and suggests that PGBM2 may be underrecognized.

MUSCLE BIOMARKERS

Abstract P180 - Cod. 143500

WEARABLE INERTIAL SENSORS IMPLEMENTATION IN MOTOR FUNCTION ASSESSMENT OF DUCHENNE MUSCULAR DYSTROPHY: STUDY PROTOCOL AND RESULTS FROM A PILOT LONGITUDINAL STUDY IN A PEDIATRIC COHORT

D'Alessandro R.^{*1}, Cavallina I.¹, Panero E.¹, Sertori F.¹, Rossi F.¹, Rolle E.¹, Monagheddu L.¹, Mongini T.E.³, Gastaldi L.², Ricci F.S.¹

¹ Department of Public Health and Pediatric Sciences, Section of Child and Adolescent Neuropsychiatry, University of Turin, Turin, Italy, Turin, Italy,

² Department of Mechanical and Aerospace Engineering, "Politecnico di Torino", Turin, Italy, Turin, Italy, ³ Department of Department of Neurosciences RLM, Neuromuscular Unit, University of Turin, Italy., Turin, Italy

The advent of disease-modifying therapies in neuromuscular disorders (NMDs) has shifted the focus toward new motor outcome measures. In this context, inertial measurement units (IMUs) have become increasingly relevant for detecting subtle motor changes in both domestic and clinical settings.

A pilot study started in February 2025 at "Regina Margherita" Pediatric Hospital in Turin to design a protocol for the implementation of IMUs during the 6-Minute Walk Test (6MWT). Four APDM OPAL IMUs were positioned to detect kinematic and spatio-temporal parameters (STPs). Results of 6MWT implementation in a sub-cohort of children affected by DMD are reported. STPs were normalized for comparisons.

At baseline, 10 male children, with a median age of 10.05 years (IQR 4.73), were enrolled. The median North Star Ambulatory Assessment (NSAA) score was 28.50 (IQR 17.00), and the median 6-Minute Walk Test (6MWT) distance was 436.00 m (IQR 116.00). Normalized Step Length and Step Time showed strong and statistically significant correlations with both the Normalized 6MWT distance and NSAA total score (for the 6MWT: $\rho = 0.976$, $p < 0.001$, and $\rho = -0.755$, $p = 0.012$; for the NSAA: $\rho = 0.856$, $p = 0.002$, and $\rho = -0.644$, $p = 0.044$). A moderate correlation was observed between Normalized Cadence and Normalized 6MWT distance ($\rho = 0.681$, $p = 0.030$). A moderate correlation approaching statistical significance was observed between the pelvic range of motion (ROM) on the frontal axis and the Normalized 6MWT distance. STPs remained constant between the start and the end of 6MWT, except for the double support ratio. At the six-month follow-up, the measurements in two patients were consistent with the previously reported correlations, supporting the reproducibility of the sensor-derived data.

IMUs implementation during 6MWT was feasible and the strong significant correlations found support the validity of the sensor-based data, warranting further longitudinal analysis.

MUSCLE BIOMARKERS

Abstract P182 - Cod. 143506

MUSCLE INVOLVEMENT IN PRIMARY SYSTEMIC AMYLOIDOSIS

Iaquinta G.^{*1}, Loprieno S.¹, Lencioni M.², Ciurli B.³, Ali G.⁴, Montano V.¹, Schirinzi E.¹, Barison A.⁵, Vergaro G.⁵, Emdin M.⁵, Siciliano G.¹, Ricci G.¹

¹ Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, ² UO Chirurgia Plastica, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy., Pisa, Italy, ³ Laboratory of Molecular genetics, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy, Pisa, Italy, ⁴ UO Anatomia Patologica, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy., Pisa, Italy, ⁵ Scuola Superiore Sant'Anna e Fondazione Toscana Gabriele Monasterio, Pisa, Italy, Pisa, Italy

Amyloidoses are a group of disorder which results from extracellular deposition of amyloid, an insoluble fibrillar material derived from various precursor proteins that self-assemble with highly ordered abnormal B-sheet conformation. The most common types of amy-

loidosis are light chain (AL) amyloidosis and wild-type (wtATTR) and hereditary (hATTR) transthyretin amyloidosis.

Amyloid deposition can occur in multiple tissues and organs, leading to organ dysfunction.

In this study we performed and analysed muscle biopsies in patients with confirmed or suspected cardiac amyloidosis. The biopsies were performed from quadriceps muscle of the left thigh. Deposition of amyloid was conducted by researching the characteristic green birefringence under polarized light following Congo red staining.

Five patients with suspected or confirmed cardiac amyloidosis underwent muscle biopsy. Amyloid deposition in skeletal muscle was confirmed in 2 patients, both without clinical signs of muscle involvement. The deposition was observed in the interstitium, and other myopathic changes observed were mild and nonspecific.

Cardiac involvement is the major cause of mortality in amyloidosis; it occurs in about 50% of patients with AL amyloidosis and is predominant in ATTR amyloidosis, typically resulting in a restrictive cardiomyopathy. Another feature of AL amyloidosis and some types of hATTR is the amyloid peripheral neuropathy, that is predominantly axonal and involves both the small and large fibres. Muscle involvement represent a recognised but rare manifestation of amyloidosis. In fact myopathy can be an early manifestation of amyloidosis. Amyloid myopathy caused by light chain amyloid deposition in muscle tissue is characterized by proximal weakness with limb-girdle distribution. However, amyloid deposition in muscle are not specific for systemic amyloidosis, but may also be seen in several hereditary muscle diseases.

Our preliminary study investigates if skeletal muscle can be a target of deposition of amyloid fibril and if the muscle biopsy can have a role in the diagnostic workout of systemic amyloidosis

MUSCULAR DYSTROPHIES

Abstract P184 - Cod. 143142

A HOMOZYGOUS PLEC VARIANT EXPANDING THE CARDIAC PHENOTYPE OF PLECTINOPATHY

Lombardi M.*³, Madonia N.³, Pizzamiglio C.¹, Comi C.³, Mazzini L.³, D'Alfonso S.², Corrado L.², De Marchi F.³

¹ Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ² Department of Health Sciences, Interdisciplinary Research Center of Autoimmune Diseases, University of Piemonte Orientale, Novara, Italy, ³ Neurology Unit, AOU Maggiore della Carità, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy

Pathogenic variants in PLEC, encoding the cytoskeletal linker protein plectin, cause a heterogeneous group of disorders ("plectinopathies") primarily affecting skin and skeletal muscle. Limb-girdle muscular dystrophy type R17 (LGMDR17) may occur without skin involvement, while cardiac manifestations are rarely reported. The phenotypic spectrum of adult-onset PLEC-related disease remains therefore incompletely defined.

To describe the clinical, histopathological, and genetic features of an adult-onset PLEC-related myopathy associated with cardiac arrhythmia and atypical muscle biopsy findings, and to expand the known

phenotypic spectrum of plectinopathies.

We report a 59-year-old woman with a 10-year history of slowly progressive limb-girdle weakness, mild bilateral ptosis, and distal upper limb involvement. Medical history was notable for Brugada syndrome, conduction abnormalities, and mild cardiomyopathy. Creatine kinase was mildly elevated, electromyography showed a myopathic pattern, and muscle biopsy revealed fibre size variability, central nuclei, COX-negative fibres, and numerous ragged-red fibres, suggesting mitochondrial dysfunction. Whole-exome sequencing identified a previously unreported homozygous PLEC deletion (c.11584_11622del; p.Arg3862_Leu3874) in exon 32, classified as likely pathogenic according to ACMG criteria. No other pathogenic variants associated with limb-girdle myopathy were detected.

This case highlights a chameleonic adult-onset PLEC-related phenotype combining limb-girdle myopathy, ptosis, IBM/mitochondrial-like histopathology, and cardiac arrhythmia consistent with Brugada syndrome. Our findings broaden the clinical spectrum of plectinopathies and underscore the importance of considering PLEC mutations in patients with multisystem neuromuscular and cardiac involvement.

MUSCULAR DYSTROPHIES

Abstract P186 - Cod. 143425

ACCAPED SCALE: AN ADDITIONAL TOOL TO DESCRIBE THE DEGREE OF DISABILITY IN RARE PEDIATRIC-ONSET NMDS?

Lambertini E.*¹, Briganti E.², Giannotta M.¹, Scarpini G.¹, Trentin F.¹, Polizzi S.⁵, Cordelli D.M.², Pirinu M.³, Ercolano A.P.⁴, Pini A.¹

¹ Pediatric Neuromuscular Unit, UOC Neuropsichiatria dell'Età Pediatrica, IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ² Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy, ³ Rehabilitation Unit, Meyer Children's Hospital, Florence, Italy, ⁴ Department of Biomedical Sciences, University of Padua, Padua, Italy, ⁵ Data Science and Bioinformatics Laboratory, IRCCS Institute of Neurological Sciences of Bologna, Bologna, Italy

In 2019, we launched a diagnostic-therapeutic care pathway for rare pediatric-onset neuromuscular disorders (NMDs) to define the healthcare process at both tertiary and local centers in Emilia-Romagna. Within this pathway, a new tool was introduced: the ACCAPED Scale. This is an assessment form for complex clinical care needs in pediatrics and is used to determine whether a referral to the Pediatric Palliative Care (PCC) network is required. This tool is quite new and is currently used intermittently. Furthermore, correlation analysis between the ACCAPED Scale and clinical-functional indicators has not yet been conducted.

This study aims to explore whether the ACCAPED Scale is consistent with patients' motor and cardiorespiratory functional status in pediatric-onset NMDs.

Retrospective data were collected from 39 patients (33 male, 6 female) aged between 4 and 17 years with genetically confirmed muscular dystrophies (BMD: 6; DMD: 17; DM1: 6; MDC1A: 3; collagen VI deficiency-related CMD: 2; LGMD: 5) and analyzed the correlation between their ACCAPED Scale index and functional motor scores (NSAA, 6MWT, 10MWT and PUL 2.0), as well as indicators

of cardiorespiratory function (EF, FVC, FEV1 and PEF). Our findings show a positive correlation between the ACCAPED Scale index and the degree of disability described by the functional motor and cardiorespiratory function scales scores.

The ACCAPED Scale may be a useful instrument to describe the degree of physical disability in patients with muscular dystrophies and could also be used as an agile communication tool between tertiary centers, PCC network and primary care.

MUSCULAR DYSTROPHIES

Abstract P188 - Cod. 143428

COMPARATIVE ANALYSIS OF LONG-TERM EFFECTIVENESS OF VAMOROLONE VS STANDARD OF CARE GLUCOCORTICOID (SOC GC) TREATMENT IN BOYS WITH DMD

Mcdonald C.M.¹, Childs A.², De Waele L.³, Gresko E.⁴, Guglieri M.⁵, Haberlova J.⁶, Hasham S.⁷, Katsalouli M.⁸, Leinonen M.⁴, Linden A.⁴, Mercuri E.*¹⁰, Muntoni F.⁹, Nevo Y.¹¹, Niks E.H.¹², Ward L.M.¹³

¹ University of California Davis Health, Davis, CA, United States of America, ² Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, ³ University Hospitals Leuven, Child Neurology; KU Leuven, Department of Development and Regeneration, Leuven, Belgium, ⁴ Santhera Pharmaceuticals, Pratteln, Switzerland, ⁵ The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, ⁶ Department of Pediatric Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic, ⁷ ~ Pratteln, Switzerland, ⁸ Pediatric Neurology Department, St. Sophia's Children's Hospital, Athens, Greece, ⁹ Dubowitz Neuromuscular Centre, Great Ormond Street Institute of Child Health; NIHR Great Ormond Street Hospital Biomedical Research Centre, London, United Kingdom, ¹⁰ Catholic University of Sacred Heart; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, ¹¹ Faculty of Medicine, Tel Aviv University; Institute of Pediatric Neurology, Schneider Children's Medical Center of Israel, Tel Aviv; Petach Tikva, Israel, ¹² Department of Neurology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands, ¹³ Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, Canada

Vamorolone demonstrated efficacy for DMD treatment in short-term studies; however, long-term durability remains unknown

To assess the long-term effectiveness and anthropometric changes in boys with DMD on vamorolone compared with SoC-GCs.

Methods: Corticosteroid-naïve children with DMD treated with vamorolone with > 1 year of exposure and follow-up in VISION-DMD (NCT03439670) and VBP15-002/003/LTE (NCT02760264/NCT02760277/NCT03038399) studies and entered continued access programs before GUARDIAN (NCT06713135) were included. Pooled data from external studies (FOR-DMD [NCT01603407]; CINRG Duchenne Natural History Study [NCT00468832]) were propensity score matched for comparison. Loss of ambulation (LoA) was analysed by time to event (TTE); slope analysis was used for anthropometry.

The mean(SD) baseline age for TTE analysis was 5.8(1.0) (vamorolone; N = 81) and 6.1 (1.2) years (SoC-GCs; N = 287), and for anthropometric analysis 5.8(1.0)(vamorolone; N = 110) and 5.9(1.1) years (SoC-GCs; N = 199). Cohorts had median drug exposures of ~5

years on vamorolone vs ~4.5 years on SoC-GCs. All drug exposures were daily. Most boys on vamorolone received 4-6mg/kg/day, with exposures of 306 (TTE) and 410 (anthropometric) patient-years and 84 (TTE) and 107 (anthropometric) for 2 mg/kg/day.

No difference was seen in time from treatment start to LoA between vamorolone and pooled SoC-GCs, nor deflazacort or prednisone separately, with hazard ratios (HR) of 1.05(95%CI 0.53;2.10), p = 0.9041; 1.22(0.57;2.60), p = 0.6544; and 0.92(0.44;1.94), p = 0.8587, respectively. Vamorolone maintained normal growth whereas growth deceleration was observed on SoC-GCs (p < .0001). There was no difference in BMI Z-score increases between vamorolone and SoC-GCs over time or in weight-to-height trajectories.

Comparable effectiveness of vamorolone to SoC-GCs was observed while preserving growth for ~5 years.

MUSCULAR DYSTROPHIES

Abstract P190 - Cod. 143124

DEEP INTRONIC CAPN3 VARIANTS AS A HIDDEN CAUSE OF LGMDR1: A CASE REPORT WITH FUNCTIONAL VALIDATION

Strafella C.*¹, Frezza E.², Goglia M.², Ferese R.³, Mela J.¹, Peconi C.¹, Zampatti S.¹, Gambardella S.⁴, Massa R.², Giardina E.⁵

¹ UOC Diagnostica di Laboratorio e Genomica Medica, Santa Lucia Foundation IRCCS, Rome, Italy, ² Neuromuscular Diseases Unit, Policlinico Tor Vergata; Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ³ Neurology Unit, IRCCS Neuromed, Pozzilli, Italy, ⁴ Neurology Unit, IRCCS Neuromed; Department of Biomolecular Sciences, University of Urbino "Carlo Bo", Urbino, Italy, ⁵ UOC Diagnostica di Laboratorio e Genomica Medica, Santa Lucia Foundation IRCCS; Department of Biomedicine and Prevention, Tor Vergata University, Rome, Italy

Calpainopathy (LGMDR1) is one of the most common forms of recessive Limb-Girdle Muscular Dystrophy (LGMD) and is typically caused by biallelic pathogenic variants in CAPN3. Nevertheless, a proportion of clinically suggestive cases remain genetically unresolved after standard analyses, raising the possibility of hidden pathogenic mechanisms.

Here, we present the case of a 56-year-old male with persistent hyperCKemia since the age of 23 years and progressive pelvic girdle weakness from 35 years, in the absence of family history.

First-tier NGS sequencing performed by Illumina NextSeq 550 system identified a heterozygous CAPN3 variant (c.2242C > T, p.Arg748Ter) previously reported in association with LGMDR1, but failed to detect a second pathogenic allele. MLPA analysis with SALSA kit P176 excluded the presence of exon deletions/duplications in the patient. Exome reanalysis subsequently revealed a deep intronic heterozygous variant (c.1537-29A > T) located far from canonical splice sites. Segregation analysis demonstrated that the two variants were inherited in trans from healthy carrier parents, supporting a recessive inheritance pattern. Functional assessment of the intronic change using a minigene assay (pSPL3 minigene vector) showed a deleterious splicing effect, inducing skipping of exon 13 and predicting a disrupted CAPN3 protein.

In line with recent studies, this case provides functional evidence that

deep intronic variants can represent a disease-causing mechanism in LGMDR1 and highlights the importance of extended genomic analyses and functional validation to resolve unexplained LGMDR1 cases.

MUSCULAR DYSTROPHIES

Abstract P192 - Cod. 143475

FIRST ITALIAN CASE OF LGMD-R26 DUE TO A NOVEL HOMOZYGOUS NONSENSE VARIANT IN POPDC3

Ferrero V.^{1,2}, Capece G.², Sogus E.², Petrosino A.², Fornasier T.², Cerfeda S.², Vianello S.², Bertolin C.¹, Salviati L.¹, Pegoraro E.², Bello L.²

¹ Unità di Genetica Medica, Dipartimento di Salute della Donna e del Bambino, Università degli Studi di Padova, Padova, Italy, ² Dipartimento di Neuroscienze DNS, Università degli Studi di Padova, Padova, Italy

We describe the case of a 65-year-old man, born to Italian parents with no known consanguinity, with a negative family history for neuromuscular disorders. At the age of 55, he presented localized atrophy and weakness at the left quadriceps femoris, which was progressive over the years, but remained isolated with no overt clinical involvement of other muscle groups. Left thigh weakness caused postural instability and difficulty climbing steps with the left leg. CK levels oscillated between approximately 2000 and 5000 U/L. A muscle biopsy (age 60, right vastus lateralis) showed atrophic and hypertrophic fibers,

a moderate increase of endomysial connective tissue and marked increase of perymysial connective tissue, and some lobulated fibers. EMG showed myogenic alterations in lower limb muscles. NGS revealed a homozygous nonsense variant in the Popeye domain containing-3 (POPDC3) gene, c.79G>T, p.Gly27Ter, consistent with a diagnosis of limb girdle muscular dystrophy type R26. Causative variants so far described in LGMD-R26 include biallelic missense and splicing variants. This patients' homozygous nonsense variant was absent from online sequencing databases, and this represents the first reported case of LGMD-R26 in an Italian patient. Furthermore, this patient's asymmetric and selective involvement of the quadriceps femoris differs from cases described in the literature, expanding the phenotypic spectrum of this recently described neuromuscular disease.

MUSCULAR DYSTROPHIES

Abstract P194 - Cod. 143073

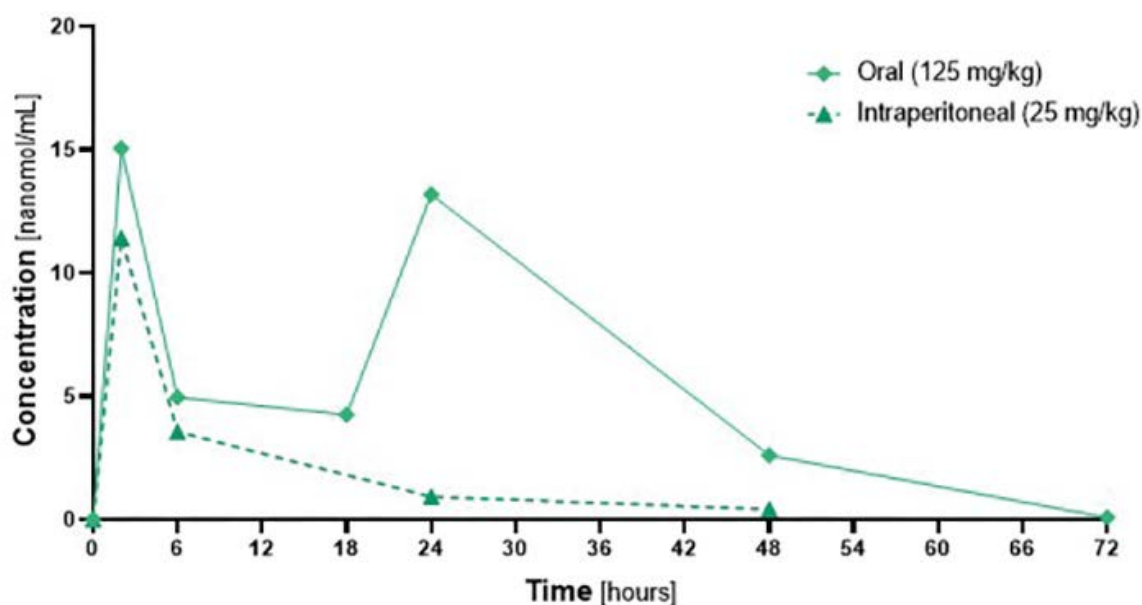
FROM PROTEIN MISFOLDING TO THERAPY: ORAL ADMINISTRATION OF THE CORRECTOR C17 IN SARCOGLYCANOPATHIES

D'Albore M.¹, Benetollo A.¹, Biasutto L.², Dalla Barba F.¹, Carotti M.¹, Sandonà D.¹

¹ Department of Biomedical Sciences, University of Padova, Padova, Italy,

² National Research Council, Neuroscience Institute, Padova, Italy

Sarcoglycanopathies are autosomal recessive muscular dystrophies



Pharmacokinetic profile of C17 after oral and intraperitoneal administration. Concentration versus time profile in blood plasma. For the oral administration C17 was administered acutely after the dissolution in PEG350, while for the intraperitoneal route in 5% DMSO, 5% Kolliphor EL physiological solution. Reported are mean values (N = 3).

caused by mutations in sarcoglycans (SGs) that assemble into a key tetrameric complex at the sarcolemma of striated muscle fibers. Most disease-causing mutations are missense variants that lead to protein misfolding and premature degradation of SGs via the endoplasmic reticulum-associated degradation pathway. Loss or reduction of a single SG destabilizes the complex, resulting in sarcolemma fragility and progressive muscle degeneration. In vitro and in vivo studies have demonstrated that C17, a small molecule belonging to the CFTR modulator family, acts as a protein corrector capable of rescuing SG expression, restoring sarcolemmal localization and improving muscle function.

Notably, in vivo efficacy was shown in a sarcoglycanopathy mouse model following chronic intraperitoneal administration. Given the promising therapeutic potential of C17, we aim to advance its translational development by investigating more clinically feasible routes of administration.

Specifically, we assessed the pharmacokinetics of C17 following oral administration. A preliminary acute oral gavage study was conducted using higher doses than those employed for i.p. administration to compensate for possible reduced bioavailability. Notably, absorption and distribution analyses revealed higher C17 concentrations in target tissues compared with i.p. These encouraging findings enabled us to reduce the doses of the compound to optimize the treatment regimen.

Successful completion of these studies will enable development of a novel protocol to evaluate the effects of chronic oral delivery of C17 through the diet. This strategy may support a more patient-friendly therapeutic regimen, reducing the need for repeated injections and improving long-term treatment compliance.

MUSCULAR DYSTROPHIES

Abstract P196 - Cod. 143043

LGMD TNPO3-RELATED SYNDROME IN A SPORADIC SLOVAKIAN PATIENT WITH A NOVEL MUTATION: A MORPHOLOGICAL STUDY

Cenacchi G.^{*1}, Angelini C.², Tonin P.³, Rodriguez Bermejo A.A.⁴, Neri L.M.⁵, Vattermi G.³

¹ Dept. of Biomedical and Neuromotor Sciences, Alma Mater University of Bologna, Bologna, Italy, ² University of Padova, Padova, Italy, ³ Dept. of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Verona, Italy, ⁴ University of Deusto, Bilbao, Spain, ⁵ Dept. of Translational Medicine, Electron Microscopy Center, University of Ferrara, Ferrara, Italy

LGMDs are variable in terms of age at onset, progression, and severity; histopathological features are muscle degeneration with connective tissue substitution. LGMDs do not share a common pathological mechanism. One of the dominant LGMDs is caused by mutation in the TNPO3 gene (LGMD D2), encoding for transportin-3, belonging to the importin beta-superfamily, mediating the nuclear import of SR proteins involved in mRNA metabolism and splicing. TNPO3-LGMD D2 was identified in an Italo-Spanish family; new affected families and sporadic cases have been described.

We report a novel 31yrs male Slovakian patient, with LGMD features entertaining an hypothesis regarding the "locking" symptoms of LGMD D2 patients: a pathogenic stop codon variant c.2686 in a heterozygous state in the TNPO3 gene and a c23335 heterozygous mutation in the gene WASHC5 associated to spastic paraplegia type 8 were detected. He developed muscle weakness and suffered since a child from many infections, without specific immune disorders. Spirometry, MRI, and EMG were performed. Biopsy of quadriceps muscle was done.

Light microscopy showed mild fiber size variability, atrophic fibers, few COX-negative fibers, a reduction of type 1 fibers and few undifferentiated fibers. Electron microscopy showed swollen mitochondria with fragmented cristae and autophagolysosomal vacuoles. Nuclei showed a clear nucleoplasm with finely distributed chromatin. Morphological and clinical data support the hypothesis that LGMD-D2 is caused by mechanisms involving cell differentiation and nuclear transport.

MUSCULAR DYSTROPHIES

Abstract P198 - Cod. 143433

LONG-TERM IMPACT OF VAMOROLONE ON BONE HEALTH COMPARED TO STANDARD OF CARE GLUCOCORTICOIDS (SOC-GC) IN BOYS WITH DUCHENNE MUSCULAR DYSTROPHY (DMD)

Guglieri M.¹, Childs A.², De Waele L.³, Gresko E.⁴, Haberlova J.⁵, Hasham S.⁴, Jaremko J.⁶, Katsaloulis M.⁷, Koujok K.⁸, Leinonen M.⁴, Linden A.⁴, Mcadam L.⁹, McDonald C.¹⁰, Mcmillan H.⁸, Mercuri E.^{*11}, Muntoni F.¹³, Nevo Y.¹², Niks E.H.¹⁴, Ward L.M.⁸

¹ The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, ² Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, ³ University Hospitals Leuven, Child Neurology; KU Leuven, Department of Development and Regeneration, Leuven, Belgium, ⁴ Santhera Pharmaceuticals, Pratteln, Switzerland, ⁵ Department of Pediatric Neurology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic, ⁶ University of Alberta, Edmonton, AB, Canada, ⁷ Pediatric Neurology Department, St. Sophia's Children's Hospital, Athens, Greece, ⁸ Children's Hospital of Eastern Ontario, University of Ottawa, Ottawa, ON, Canada, ⁹ Holland Bloorview Kids Rehabilitation Hospital, Bloorview Research Institute, University of Toronto, Toronto, ON, Canada, ¹⁰ University of California Davis Health, Davis, CA, United States of America, ¹¹ Catholic University of Sacred Heart; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, ¹² Faculty of Medicine, Tel Aviv University; Institute of Pediatric Neurology, Schneider Children's Medical Center of Israel, Tel Aviv, Petach Tikva, Israel, ¹³ Dubowitz Neuromuscular Centre, Great Ormond Street Institute of Child Health, London, United Kingdom, ¹⁴ Department of Neurology, Leiden University Medical Center, Leiden, Zuid-Holland, Netherlands

Boys with DMD on SoC-GC have high vertebral fracture (VF) risk and bone age delay.

To Indirectly compare VF and bone age delay after long-term treatment with vamorolone or SoC-GC.

Methods: Baseline data from 37 patients enrolled in GUARDIAN were propensity score matched with a previously published SoC-GC cohort

(N = 60; mostly on daily deflazacort). VF were evaluated on lateral spine x-rays using the Genant semi-quantitative methodology, Spinal Deformity Index (SDI) was calculated (sum of the Genant grades), and bone age was evaluated using hand X-rays (BoneExpert™).

At X-ray, mean $\pm$ SD ages in vamorolone (N = 37) and matched SoC-GC (N = 31) cohorts were 10.9 ± 1.25 and 11.7 ± 1.53 years. Mean drug exposure was 5.2 ± 0.95 years for vamorolone (190.6 patient-years) vs 5.4 ± 0.06 years on SoC-GC (167.5 patient-years). Mean doses $\pm$ SD at X-ray were 4.89 ± 1.28 mg/kg/day and 0.65 ± 0.21 mg/kg/day for vamorolone and deflazacort, respectively. 3/37 (8.1%) patients had 9 VF on vamorolone vs 13/31 (41.9%) with 30 VF on SoC-GC (odds ratio[95%CI]: 0.1296[0.02903,0.5789], $p = 0.0082$). Mean SDI for subjects with and without VF was lower on vamorolone vs SoC-GC (0.32 vs 1.06). Three patients with VF on vamorolone had SDI scores of 1, 3 and 8. Of thirteen patients on SoC-GC with VF, 7 had SDI of 1, and the remaining had SDIs of 3, 4 ($n = 3$), 5 and 6. Mean bone age delay was 0.8 ± 1.5 years on vamorolone vs 1.6 ± 1.6 years on SoC-GC.

VF prevalence was significantly lower with vamorolone compared with SoC-GC after ~5 years of exposure. All patients should be monitored for VF.

MUSCULAR DYSTROPHIES

Abstract P200 - Cod. 143494

PREDICTION OF NORTH STAR AMBULATORY ASSESSMENT CHANGES AT 1 AND 2 YEARS FROM BASELINE SCORE AND TIMED FUNCTION TESTS IN BECKER MUSCULAR DYSTROPHY

Roverato C.*, Fornasier T., Sogus E., Petrosino A., Mastellarò S., Gorgoglione D., Pegoraro E., Bello L.
Università degli studi di Padova, Padova, Italy

North Star Ambulatory Assessment (NSAA) is being implemented as a primary outcome in several clinical trials for Becker muscular dystrophy (BMD).

We developed an algorithm predicting NSAA trajectories over 1–2 years, based on baseline age, NSAA score, and timed function tests (TFTs: time to run/walk 10 m, rise from the floor, and climb 4 standard stairs).

From our single center retrospective database of 104 BMD patients followed up with serial motor function assessments, we selected adults with NSAA 10–32 points, age 18–50 years, and complete evaluations (NSAA and TFTs) at one- and two-year intervals ($\pm$ 2 months). We selected 24 patients (median age 34.5 years, range 18.4–48.7; median NSAA score 19, range 10–32).

The most frequently observed genetic mutations were multi-exonic deletions, predominantly involving exons 45–48 (39.1%) and 45–47 (30.4%).

Twelve- and 24-month NSAA outcomes were modeled separately using multivariable linear regression with baseline age, baseline NSAA, and timed function test velocities as fixed effects. Models included a single intercept representing the expected follow-up NSAA for an average patient; random effects were not included, as each patient

contributed one observation per timepoint.

We derived the following formulas:

NSAA 12 months = $-5.9173 + 0.0492 \cdot (\text{Age}) + 0.8707 \cdot (\text{NSAA}) + 2.9298 \cdot (10 \text{ m run walk/speed m/s}) + 3.0543 \cdot (\text{rise from floor speed s}^{-1}) - 0.0098 \cdot (4 \text{ stair climb velocity steps/s})$; and

NSAA 24 months = $-4.2016 + 0.0793 \cdot (\text{Age}) + 0.6172 \cdot (\text{NSAA}) - 1.0315 \cdot (10 \text{ m run walk/speed m/s}) + 9.7015 \cdot (\text{rise from floor speed s}^{-1}) + 4.4950 \cdot (4 \text{ stair climb velocity steps/s})$.

These algorithms may prove useful for patient counselling and/or clinical trial design. We plan validation in independent cohorts, e.g. longitudinal data from the Italian Telethon BMD Natural History study cohort.

MUSCULAR DYSTROPHIES

Abstract P202 - Cod. 142948

RESPONSIVENESS OF FUNCTIONAL ASSESSMENT SCALES IN BECKER MUSCULAR DYSTROPHY: TWO-YEAR LONGITUDINAL FOLLOW-UP

De Maria M.*¹, Zoppi D.¹, Russo A.¹, Vallefucio F.¹, Russo R.¹, Boemia V.¹, Esposito G.², Ruggiero L.¹

¹ Department of Neurosciences, Reproductive Sciences, and Odontostomatology, University of Naples "Federico II," Naples, Italy, Napoli, Italy, ² CEINGE-Biotecnologie Avanzate s.c. a r.l., Via G. Salvatore 486, 80145 Naples, Italy, Napoli, Italy

Becker muscular dystrophy (BMD) is a rare X-linked dystrophinopathy with progressive muscle weakness and heterogeneity. Longitudinal data are limited, and the responsiveness of functional and patient-reported outcomes remains unclear. Sensitive tools are needed to detect meaningful longitudinal changes.

Functional measures included the Medical Research Council (MRC), North Star Ambulatory Assessment (NSAA), North Star Assessment for Dysferlinopathy (NSAD), Performance of Upper Limb 2.0 (PUL 2.0), and the 6-Minute Walk Test (6MWT), and Individualized Neuro-muscular Quality of Life questionnaire (INQoL).

Seventy genetically confirmed BMD patients were identified at baseline; 28 with longitudinal follow-up (6–24 months) were analyzed (16 at 24 months). Mean baseline age was 27.2 ± 14.6 years (12–79). Baseline NSAA score was 30.8 ± 6.7 , NSAD 37.1 ± 6.8 , 6MWT 489.6 ± 94.8 m, and PUL 2.0 41.9 ± 0.3 . NSAA and NSAD worsened in 31.8% of patients (mean $\Delta -2.86 \pm 1.57$ and -3.29 ± 1.98 , respectively), while 6MWT declined in 42.9% (-44.0 ± 28.0 m). PUL 2.0 worsened in only one patient, confirming marked ceiling effects. Only 7.1% showed uniform worsening, while the remainder remained stable or discordant. INQoL revealed mismatch between patient-reported burden and objective measures.

Overall, heterogeneity and discordance indicate that no single outcome adequately captures disease progression in BMD.

Greater decline in 6MWT/NSAA and PUL 2.0 ceiling effects underscore the need for multidimensional, responsive outcomes integrated with patient-reported measures in future trials.

MUSCULAR DYSTROPHIES**Abstract P204 - Cod. 142737****THE CAPN3 P.ASP753ASN VARIANT: EVIDENCE SUPPORTING A PATHOGENIC ROLE IN AUTOSOMAL DOMINANT LIMB-GIRDLE MUSCULAR DYSTROPHY**

D'Este G.¹, Giorgetti A.², Cassandrini D.³, Magri F.⁴, Ronchi D.⁵, Rubegni A.⁶, Lopercolo D.⁷, Malandrini A.⁷, Merlini L.⁸, Vattermi G.⁹, Tonin P.⁹, Barresi R.*¹

¹IRCCS San Camillo Hospital, Venezia, Italy, ²Department of Biotechnology, University of Verona, Verona, Italy, ³UOC Immunologia, Azienda Ospedaliera Universitaria Integrata, Verona, Italy, ⁴IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Neuromuscular Unit, Milano, Italy, ⁵IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Neurology Unit, Milano, Italy, ⁶IRCCS Stella Maris Foundation, Pisa, Italy, ⁷Department of Medicine, Surgery and Neurosciences, University of Siena, Siena, Italy, ⁸Department of Biomedical and Neuromotor Science, DIBINEM, University of Bologna, Bologna, Italy, ⁹Department of Neurosciences, Biomedicine and Movement Sciences, Section of Clinical Neurology, University of Verona, Verona, Italy

Calpain3 (CAPN3) is a muscle-specific calcium-dependent protease essential for sarcomere maintenance. Biallelic CAPN3 variants cause recessive limb-girdle muscular dystrophy type R1 (LGMDR1). Increasing evidence suggests that heterozygous CAPN3 variants may also be associated with an autosomal dominant form, LGMD4; however, pathogenic mechanisms remain poorly understood and validated functional assays are lacking.

To reassess the clinical and molecular significance of monoallelic CAPN3 variants, we analyzed a multicenter Italian cohort of unrelated patients carrying single CAPN3 variants, in whom additional pathogenic alleles were excluded using complementary molecular approaches. Clinical, biochemical, histopathological, and structural data were analysed.

The missense variant c.2257G > A (p.Asp753Asn) was identified in eight unrelated individuals aged 6-80 years, representing the most recurrent variant in the cohort. Clinical presentations ranged from asymptomatic hyperCKemia and exertional myalgia to mild limb-girdle and axial weakness. Muscle biopsies showed mild, nonspecific myopathic features with variable reduction of CAPN3 expression. Structural modeling revealed that Asp753 lies within the C-terminal Ca²⁺-binding region, where it stabilizes the Ca²⁺-bound active conformation via electrostatic inter-domain interactions; substitution with asparagine is predicted to weaken these interactions, impairing calcium-dependent activation and protease regulation. A literature review identified 31 additional cases worldwide, confirming recurrence and marked phenotypic heterogeneity.

Our findings support a pathogenic role for the CAPN3 p.Asp753Asn variant in autosomal dominant LGMD4. They also underscore the diagnostic challenges posed by single CAPN3 variants and highlight the need for integrated clinical, molecular, and functional studies to better define dominant CAPN3-related disease mechanisms.

MUSCULAR DYSTROPHIES**Abstract P206 - Cod. 143482****THE MANY FACES OF LIMB-GIRDLE MUSCULAR DYSTROPHIES: INSIGHTS FROM A LARGE SINGLE-CENTER COHORT IN SOUTHERN ITALY**

Zoppi D.*¹, Russo A.¹, Vallefucio F.¹, De Maria M.¹, D'Amico E.¹, Russo R.¹, Boemia V.¹, Esposito G.², Ruggiero L.¹

¹ Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy., Napoli, Italy,

² Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II", Naples, Italy. & CEINGE-Biotecnologie Avanzate Franco Salvatore, Naples, Italy., Napoli, Italy

Limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group of hereditary myopathies.

We retrospectively analyzed clinical, genetic, histopathological, electrophysiological, and imaging data from 63 genetically confirmed LGMD patients of a Southern Italian referral center.

Fifteen subtypes involving 14 genes were identified. The most prevalent were calpainopathy (CAPN3, n = 18, 26.1%), anoctaminopathy (ANO5, n = 12, 17.4%), and dysferlinopathy (DYSF, n = 8, 11.6%). Median age at onset was 22 years (range 1–59); asymptomatic hyperCKemia was the presenting feature in 54.0%. Peak CK differed significantly across genotypes (Kruskal-Wallis p = 0.019) and inversely correlated with age at onset (Spearman rho = -0.49, p = 0.001). At last evaluation, 74.6% retained independent ambulation. Earlier onset was significantly associated with loss of ambulation (median 10 vs 30 years, p = 0.013). Scapular girdle weakness (p = 0.005) and distal upper (p < 0.001) and lower limb involvement (p = 0.010) were significantly associated with wheelchair dependence. Cardiomyopathy (7.5%) and non-invasive ventilation (5.5%) were uncommon. Muscle biopsy, performed in 73%, showed dystrophic or myopathic changes in 94%, notably, ANO5 patients had significantly fewer dystrophic biopsies (p = 0.007). Electromyography revealed a myopathic pattern in 59.4%, though 40.6% had normal findings, particularly in ANO5 (66.7%). Muscle MRI, available in 32%, demonstrated fatty replacement in 75%; STIR positivity was found in only one dysferlinopathy case.

Our cohort confirms the marked genetic heterogeneity of LGMDs. Asymptomatic hyperCKemia as the most common presenting feature reinforces the role of genetic testing in pauci-symptomatic patients. Normal EMG and biopsy in a subset, particularly LGMD-R12, underscore that standard workup may be insufficient without molecular confirmation.

MUSCULAR DYSTROPHIES**Abstract P208 - Cod. 142942****TRANSITION TO ADULTHOOD IN PEOPLE WITH DYSTROPHY: SOCIAL COGNITION MECHANISMS, PSYCHOSOCIAL ADJUSTMENT, AND MENTAL HEALTH AND COPING**

STRATEGIES (TAMDY - CLINICALTRIALS.GOV IDENTIFIER: NCT07101185)

Colombo N.^{*1}, Canella G.², Nobile M.¹, Bello L.³, Berardinelli A.⁴, Brolatti N.⁵, Casiraghi J.⁶, Carraro E.⁷, Coccia M.⁸, Cristofani P.⁹, Delle Fave A.¹⁰, Filosto M.¹¹, Maggi L.²¹, Magri F.¹², Mercuri E.M.¹³, Mongini T.¹⁴, Previtali S.¹⁵, Ricci G.¹⁶, Sframeli M.¹⁷, Trabacca A.¹⁸, Urgesi C.¹⁹, Valentino M.L.²⁰, D'angelo M.G.²

¹ Scientific Institute IRCCS E. Medea, Child Psychopathology Unit, 23842 Bosisio Parini, LC, Italy, ² Scientific Institute, IRCCS E. Medea, Unit of Rare Diseases of the Central and Peripheral Nervous System, 23842 Bosisio Parini, LC, Italy, ³ Department of Neuroscience DNS, University of Padova, 35128 Padua, Italy, ⁴ Child and Adolescence Neuromuscular Disorders Research Section, IRCCS Mondino Foundation, 27100 Pavia, Italy, ⁵ IRCCS Istituto Giannina Gaslini, 16147 Genoa, Italy, ⁶ The NeMO Clinical Center in Milan, 20162 Milan, Italy, ⁷ Scientific Institute IRCCS E. Medea, Conegliano Research Centre, 31015 Conegliano, TV, Italy, ⁸ NeMO Clinical Center Ancona - Azienda Ospedaliero-Universitaria Delle Marche, 60126 Ancona, Italy, ⁹ Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, 56128 Calambrone, Pisa, Italy, ¹⁰ Department of Pathophysiology and Transplantation, University of Milano, 20122 Milan, Italy, ¹¹ NeMO-Brescia Clinical Center for Neuromuscular Diseases, 25064 Brescia, Italy, ¹² Neurology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy, ¹³ Fondazione Policlinico Universitario Agostino Gemelli, 00168 Rome, Italy, ¹⁴ Neuromuscular Unit, Department of Neurosciences RLM, University of Torino, 10124 Torino, Italy, ¹⁵ Vita-Salute San Raffaele University, 20132 Milan, Italy, ¹⁶ Department of Clinical and Experimental Medicine, University of Pisa, 56126 Pisa, Italy, ¹⁷ Department of Clinical and Experimental Medicine, Unit of Neurodegenerative Diseases, University Hospital "G. Martino", 98122 Messina, Italy, ¹⁸ Scientific Institute IRCCS E. Medea, Unit for Severe Disabilities in Developmental Age and Young Adults (Developmental Neurology and Neurorehabilitation), 72100 Brindisi, Italy, ¹⁹ Scientific Institute, IRCCS E. Medea, 33037 Pasian di Prato, Udine, Italy, ²⁰ IRCCS Institute of Neurological Sciences of Bologna, 40139 Bologna, Italy, ²¹ Department of Neuroimmunology and Neuromuscular Diseases, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milan, Italy

Pharmacological care and respiratory supports in Duchenne Muscular Dystrophy have increased life expectancy, resulting in a growing number of adolescents and adults with DMD who face complex medical, psychological, and social challenges. In adulthood alterations in social cognition may emerge and influence psychosocial adjustment, mental health, and coping strategies. Previous research highlights substantial individual variability in responses to stressors, suggesting heterogeneous adjustment profiles. Understanding how social cognition interacts with psychosocial functioning and clinical severity is therefore essential to improve care.

This multicentre Italian study supported by Telethon (Gup24011) aims to investigate social cognition, body image and its associations with well-being and mental health, and models the relationships between medical conditions, social cognition, and psychosocial functioning in over 250 DMD subjects. Participants are subjects older than 14 years old and their caregivers recruited from 18 centre with expertise in neuromuscular diseases. The assessment involves the use of standardized scales according to literature. Specifically, participants complete seven self-report questionnaires and caregivers complete scales evaluating psychological distress, coping strategies, and perceived burden.

A database has been created using REDCap platform for research

purposes. To date, questionnaires have been administered to 18 individuals with DMD (mean age 24.3, range 14–41) and their caregivers at the Coordinating Unit.

These preliminary evaluations confirmed the adequacy of the questionnaires and a good subject compliance with the study. Results are expected to inform personalised interventions and integrated clinical pathways aimed at improving psychological well-being, social functioning, and quality of life in individuals with DMD.

MUSCULAR DYSTROPHIES

Abstract P210 - Cod. 143023

UNEXPECTED DIAGNOSIS OF DYSTROPHINOPATHY

Marelli S.^{*}, Bonaglia M.C., Mani E., Tonelli L., Lanteri F., Bassi M.T., D'Angelo M.G.

Scientific Institute IRCCS E. Medea, Associazione La Nostra Famiglia, Bosisio Parini (Lecco), Italy

The comorbidity between dystrophinopathies and neurodevelopmental disorders and/or intellectual disability (ID) is well reported; these disorders can appear before muscular impairment and can cause delays in specific medical care.

Report cases of occasional findings of dystrophin gene mutations in individuals who accessed the child neuropsychiatry department for neurodevelopmental disorders evaluations

In a population in which genetic alterations associated with neurodevelopmental disorders are often described, in two children with a definite diagnosis of autism (ASD) and no history of motor developmental delay or muscular involvement signs, we unexpectedly found mutations in the dystrophin gene (two in frame deletion Xp21.1 respectively involving exon 45-51 and exons 43-47).

The family segregation study identified the two mothers as carriers of the mutation and one 10-year-old brother with the mutation, clinically asymptomatic.

Collaterally, the segregation study of a family in which the child diagnosed with autism and carrying a deletion on chromosome 5 of uncertain significance, showed in the mother a deletion of exons 46-48 in the DMD gene.

One 4 years old girl, evaluated for neurodevelopmental disorder, was also identified as carrying a mutation in the dystrophin gene.

On the one hand, these data support the known comorbidity between neurodevelopmental disorders and dystrophinopathies, once again highlighting the role of dystrophin in the brain.

On the other hand, they underscore the pivotal role of specific genetic analyses in pathologies such as ASD/ADHD and ID in which the close gene-disease correlation is not yet fully established, allowing new diagnosis and relative appropriate medical monitoring.

MUSCULAR DYSTROPHIES

ABSTRACT P212 - Cod. 143315

WHAT DO PATIENTS AND FAMILIES REALLY

NEED? PSYCHOLOGICAL CARE IN MUSCULAR DYSTROPHIES FROM A STAKEHOLDER PERSPECTIVE

Pratile D.C.*¹, Conti C.¹, Khalil S.¹, Gardani A.², Agosto C.³, Nesaiba A.A.⁴, Cadri S.⁵, Cumbo F.⁶, D'Amico A.⁶, De Maria M.⁷, Gadaleta G.⁸, Giannotta M.⁹, Messina S.¹⁰, Pantaleo C.¹¹, Pedemonte M.¹², Pera M.C.¹³, Pugliese M.¹⁴, Risi B.¹⁵, Rolle E.¹⁶, Trabacca A.¹⁷, Berardinelli A.²

¹ Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy, ² Child Neurology and Psychiatry Unit, IRCCS Mondino Foundation, Pavia, Italy, ³ Department of Women's and Children's Health - University of Padua, Padua, Italy, ⁴ NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy, ⁵ NeMO Clinical Center Ancona, Division of Neuromuscular Diseases, Ancona, Italy, ⁶ Unit of Muscular and Neurodegenerative Disorders, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy, ⁷ Department of Neurosciences, University of Naples Federico II, Napoli, Italy, ⁸ Neuromuscular Unit, Department of Neurosciences 'Rita Levi Montalcini', University of Turin, Turin, Italy, ⁹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Neuromuscular Pediatric Unit, Bologna, Italy, ¹⁰ Unit of Neurodegenerative Disorders, Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy, ¹¹ UILDM - Italian Union for Muscular Dystrophy, Ravenna Section, Ravenna, Italy, ¹² Pediatric Neurology and Muscle Diseases Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy, ¹³ Child Neuropsychiatry Unit, Department of Medicine and Surgery, University of Parma, Parma, Italy, ¹⁴ Parent Project aps, Rome, Italy, ¹⁵ NeMO-Brescia Clinical Center for Neuromuscular Diseases, Brescia, Italy e Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, ¹⁶ Section of Child and Adolescent Neuropsychiatry, Department of Public Health and Paediatric Sciences, University of Turin, Turin, Italy, ¹⁷ Unit for Severe Disabilities in Childhood and Young Adulthood (Developmental Neurology and Neurorehabilitation), Scientific Hospital of Neurorehabilitation, "La Nostra Famiglia" Association - IRCCS Eugenio Medea, Brindisi, Italy

In recent years, advances in medical treatment have significantly improved prognosis and life expectancy in individuals with muscular dystrophies (MD). However, psychological, emotional, and social needs of patients and their families often remain under-recognized. Progressive loss of autonomy, complex care pathways, and long-term uncertainty impact not only patients but also caregivers, who frequently experience emotional burden and unmet support needs.

Our project aims to systematically explore psychological, emotional, and psychosocial needs of individuals with MD and their caregivers, in order to identify unmet needs and define shared priorities for psychological support within neuromuscular care.

LIGHT-MD adopts a participatory, multiprofessional approach using the Delphi methodology. Patients (6–30 years), caregivers, and healthcare professionals (neurologists, child neuropsychiatrists, pediatricians, psychologists/psychotherapists/neuropsychologists, physiotherapists, social workers, and patient associations) are involved in a three-step process. Phase 1 collects qualitative data through open-ended questions exploring emotional experiences, daily challenges, resources, and perceived gaps in care. Phase 2 involves thematic analysis and synthesis of responses by an independent working group, followed by feedback from participants. Phase 3 quantifies consensus, asking stakeholders to rank identified areas according to relevance and priority.

The study is expected to identify shared and group-specific psychosocial needs across patients, caregivers, and professionals, highlighting

priority areas for intervention and gaps in current care pathways. LIGHT-MD proposes an innovative, stakeholder-driven framework to guide psychological healthcare in MD. By integrating patient, caregiver, and professional perspectives, the project aims to inform practical, evidence-based guidelines and promote more person-centered, integrated neuromuscular care.

MYOTONIC DYSTROPHIES

Abstract P214 - Cod. 143823

EXPERIENCES WITH MYOTONIC DYSTROPHY TYPE 1 (DM1) AND TREATMENT WITH DEL-DESIRAN: INTERVIEWS WITH PARTICIPANTS IN MARINA-OLE™ AND THEIR CAREGIVERS

Davidson A.M., Gallagher K.P., Vaziri S., Knisely B., Army C., Fowler M.*

Avidity Biosciences, Inc., San Diego, United States of America

Myotonic dystrophy type 1 (DM1) is a rare, dominantly inherited progressive neuromuscular disorder. Delpacibart etedesiran (del-desiran; AOC 1001) is an investigational antibody–oligonucleotide conjugate designed to address the underlying genetic cause of DM1. The phase 2, open-label extension MARINA-OLE™ trial evaluated long-term safety/tolerability/efficacy of del-desiran.

To gain insight into experiences of those with DM1/their caregivers and explore perceived effects of del-desiran, interviews were conducted with MARINA-OLE participants and caregivers. The qualitative study involved semi-structured interviews with MARINA-OLE participants (n = 27) and caregivers (n = 17) interviewed separately. Participants described themselves, how DM1 impacted their lives, what their lives were like before, and trial experiences. They were asked about symptoms before/during the trial using a list of 31 symptoms within 6 domains and their experiences with MARINA-OLE.

Most frequently reported DM1 concerns were myotonia, weakness, and mobility. Impacts of DM1 on daily life differed. Of 27 MARINA-OLE participants, 22 reported improvements in ≥1 DM1-related symptoms. Improvements were noted in muscle, neurologic, gastrointestinal, and metabolic functions. Domains with the most respondents reporting no improvement were psychological and social functions. Generally, interviews with caregivers followed a similar pattern. MARINA-OLE participants reported a range of DM1 symptoms across multiple domains. Most reported improvements in ≥1 DM1 symptoms. Improvement was noted with varying symptoms, a finding consistent with the heterogeneity of presentation in DM1. Understanding their experiences helps ensure patients' voices remain centered during drug development.

MYOTONIC DYSTROPHIES

Abstract P216 - Cod. 143456

MYOTONIC DYSTROPHY TYPE 1: MULTIDIMENSIONAL CLINICAL CHARACTERIZATION AND IDENTIFICATION OF

PROGNOSTIC FACTORS

De Pasqua S.*¹, Bonan L.², Avoni P.², Vacchiano V.¹, Pizza F.², Bonati E.³, Donadio V.², Giannoccaro M.P.², Rizzo G.², Liguori R.²
¹ IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy, ² DIBINEM, University of Bologna, Bologna, Italy, ³ UOC Pneumologia, Ospedale Bellaria, Bologna, Italy

Myotonic dystrophy type 1 (DM1) is a progressive multisystemic disease involving skeletal muscle, heart, respiratory and central nervous system. The natural history of many clinical aspects remains unclear and longitudinal studies applying standardized protocols are lacking. To perform a standardized multidimensional phenotypic characterization of DM1 patients through evaluation of cardiological and respiratory parameters, sleep recordings and intraepidermal nerve fiber density through skin biopsy, identifying clinical parameters with prognostic significance.

72 DM1 patients (24 E1, 41 E2, 7 E3) underwent standardized clinical evaluation including: pulmonary function tests and blood gas analysis; cardiorespiratory monitoring; ECG, Holter and echocardiography. 45 DM1 patients also underwent skin biopsy for small fiber analysis. Correlations among clinical and genotypic parameters were analyzed during 3 years of follow-up.

Respiratory function showed significant reduction in E3 patients and negative correlation with disease duration and MIRS score. Higher CVF values predicted reduced risk of cardiopathy ($p = 0.025$) and sleep apnea ($p = 0.023$). Blood gas abnormalities, sleep related breathing disorders (SRBD) and excessive daytime sleepiness were independent of genetic class and muscular impairment, suggesting central dysfunction. Cardiological involvement showed no differences among the 3 genetic classes. Skin biopsy revealed subclinical small fiber neuropathy with predominant somatic fiber involvement in 82% of patients.

Our results suggest a possible central nervous system involvement in DM1 and confirm that many multisystem aspects are, at least in part, independent of the genotype; moreover, underlying the importance of periodic multidisciplinary follow-up. These findings contribute to DM1 phenotypic characterization and may guide longitudinal studies.

MYOTONIC DYSTROPHIES

Abstract P218 - Cod. 142834

SERUM PROTEOMIC PROFILING REVEALS ACUTE INFLAMMATORY RESPONSE AS A KEY PATHOGENIC MECHANISM IN MYOTONIC DYSTROPHY TYPE 1

Abati E.¹, Benigni L.², Ottoboni L.², Sebastiani E.², Comi G.², Corti S.², Meola G.*²

¹ Fondazione IRCCS Ospedale Maggiore Policlinico, Milano, Italy, ² Università degli Studi di Milano, Milano, Italy

Myotonic dystrophy type 1 (DM1) is a multisystemic disorder caused by CTG repeat expansion, with poorly understood systemic proteomic changes. Circulating protein biomarkers could provide insights into disease mechanisms, facilitate monitoring and shed light on new potential therapeutic targets.

To characterize serum proteomic profiles across DM1 subtypes and identify differentially expressed proteins correlating with clinical manifestations and disease severity.

Methods: Cross-sectional proteomic analysis of serum from 35 DM1 patients (25 classic, 4 juvenile, 2 infantile, 4 congenital) versus 15 controls. Following protein depletion and TMT10plex labeling, mass spectrometry analysis was performed. Bioinformatics included Principal Component Analysis (PCA), differential expression analysis using limma with MIRS/sex covariates, and Gene Ontology enrichment. Differential expression identified 35 significantly dysregulated proteins (adjusted $p < 0.05$, $\log_2FCI > 0.5$). Acute inflammatory response was most enriched ($p_{adj} = 9.97 \times 10^{-19}$), involving 7 proteins. Classic DM1 showed pronounced inflammatory signature: ORM1, ORM2, A2M, HP, HPR significantly upregulated ($p < 0.0001$), APOA2 downregulated ($p < 0.001$). Congenital DM1 demonstrated severe early inflammation, juvenile DM1 intermediate changes. Disease enrichment revealed associations with acute kidney insufficiency ($p_{adj} = 1.84 \times 10^{-7}$) and drug toxicity ($p_{adj} = 1.63 \times 10^{-6}$). This first comprehensive serum proteomic study reveals acute inflammatory response as central to DM1 pathogenesis, with subtype-specific signatures suggesting distinct mechanisms. Novel kidney and drug metabolism associations expand understanding of systemic involvement. Acute phase proteins represent promising biomarkers, identifying inflammation as a potential therapeutic target beyond RNA toxicity mechanisms.

MYOTONIC DYSTROPHIES

Abstract P220 - Cod. 142993

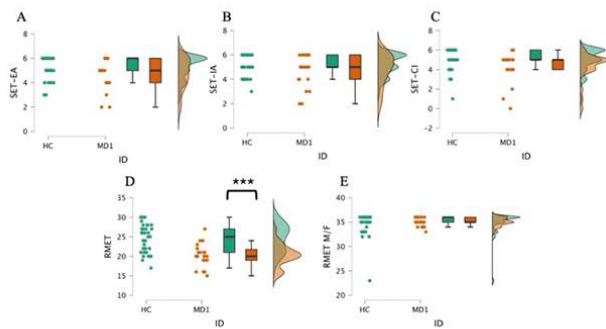
THE COGNITIVE-BEHAVIORAL MISSING LINK IN MYOTONIC DYSTROPHY TYPE 1: RETHINKING SOCIAL COGNITION ASSESSMENT

Costantini E.M.*¹, Cadri S., Ciattaglia A., Coccia M.
NeuroMuscular Omnicentre (NeMO), AOU delle Marche, Ancona, Italy

Social cognition competences have been claimed to drive the neuro-behavioral fingerprints of myotonic dystrophy type 1 (MD1). Though, evidence is limited, especially in Theory of Mind (ToM) tasks. Moreover, MD1 patients often score above pathological cut-offs at standard tasks, questioning the common measures ability to capture the real nature of the putative impairment in this domain

to test emotion recognition and ToM determining if assessment of processing speed in social cognition tasks (Reading the Mind in the Eyes Test - RMET - and the Story-Based Empathy Test - SET, both assessed in accuracy and reaction times) captures a core MD1 distinctive cognitive signature; to detect abnormal pattern of association with general cognitive abilities in respect to healthy controls (HC) and to determine if the putative social cognition impairment is specific or secondary to the general cognitive impairment (assessed by ROCF, TMT, Stroop, and verbal fluency tasks).

33 MD1 and 40 HC were tested. MD1 performed worse on RMET but comparably on SET. Reaction-times were much higher across RMET and all SET subcomponents, even after adjusting for the executive performances (TMT-B). ROC analyses confirmed superior discrimina-



tive value of timing indices over accuracy in ToM. Impairment in social cues processing speed is a core MD1 feature, only partly explained by executive dysfunction, suggesting a partially domain-specific impairment in socio-affective integration. Social reaction time measures emerge as sensitive behavioral markers with translational potential for clinical monitoring and patient-centered intervention.

FRIDAY, MAY 15TH, 2026

POSTER SESSION

Spinal Muscular Atrophy and other neuromuscular disorders even numbers

15:00-16:30

Chairs: Letizia Manneschi, Elisabetta Sette

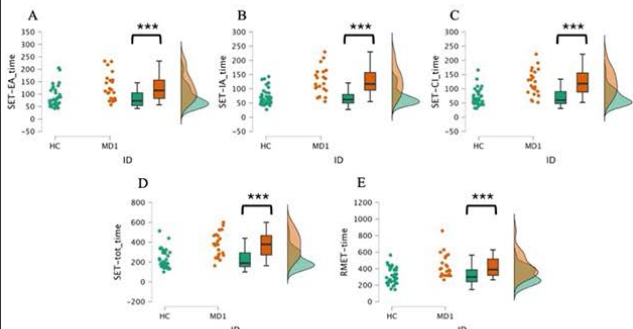
ADVANCED DIAGNOSTICS

Abstract P002 - Cod. 142618

CHARACTERIZATION AND STAGING OF CARDIOVASCULAR AUTONOMIC FAILURE IN AL AMYLOIDOSIS

Vitali F.^{1*}, Sander L.², Chiaro G.², Ingle G.², Mcnamara P.², Watson L.², Lunn M.P.³, Gillmore J.D.⁴, Iodice V.²

¹ Department of Neuroscience, Università Cattolica del Sacro Cuore, Rome, Italy, ² National Autonomic Centre, National Hospital for Neurology and Neurosurgery, London, United Kingdom, ³ Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, United Kingdom, ⁴ National Amyloidosis Centre, Division of Medicine, University College London, London, United Kingdom



Light-chain amyloidosis (AL amyloidosis) is a systemic disorder characterized by the deposition of monoclonal light-chain as amyloid fibrils, leading to multiorgan dysfunction. Cardiovascular autonomic failure (cvAF) represents a contributor to morbidity, but its natural history and staging remain poorly defined.

This retrospective study included 38 patients with biopsy-proven AL amyloidosis who underwent comprehensive autonomic testing at the National Hospital for Neurology and Neurosurgery, London. cvAF was considered stage 1 when mild parasympathetic and/or sympathetic impairment occurred without neurogenic orthostatic hypotension (nOH), and stage 2 when both domains were affected with nOH.

At onset, one-third of patients reported autonomic symptoms. At testing (T1; median disease duration: 3 years), nearly all showed cvAF. Half were classified as stage 1, with predominant parasympathetic involvement, while 47% as stage 2, with half of these experiencing orthostatic symptoms. Stage 2 patients more frequently presented gastrointestinal ($p = 0.032$) and urogenital symptoms ($p = 0.004$), and impaired norepinephrine response during head-up tilt ($p < 0.001$). Mortality and overall survival did not differ between stages. Patients with autonomic onset were more likely to develop somatic polyneuropathy ($p = 0.036$), orthostatic hypotension ($p = 0.012$), and higher orthostatic intolerance ratios at T1 ($p = 0.001$). Autonomic onset independently predicted progression to stage 2 (OR = 7.600, 95% CI 1.373–42.063, $p = 0.020$).

Cardiovascular autonomic failure is frequent in AL amyloidosis, may emerge early, and progresses with the disease course. These findings highlight the need for systematic autonomic assessment and increased awareness of pharmacological and non-pharmacological management strategies.

EXPERIMENTAL THERAPIES

Abstract P062 - Cod. 142975

EFGARTIGIMOD IN IMMUNE-MEDIATED NECROTIZING MYOPATHY: CURRENT EVIDENCE

Masuzzo F.*, Virgilio E., Demattei F., Ferri R., Matta M., Torrieri M.C., Clerico M.

A.U.O. San Luigi Gonzaga, Orbassano (TO), Italy

We report a case of a 35-year-old woman with necrotizing myopathy, in whom treatment with efgartigimod was associated with clinical stabilization.

Since the summer of 2021, the patient developed dorsiflexion weakness of the right foot, subsequently involving the left. From January 2022, proximal muscle weakness and muscle cramps appeared, with difficulty rising from a seated position to standing without support. She referred also dysphagia and ptosis.

She was first evaluated at our center in June 2022 and admitted for diagnostic work-up, including lumbar puncture, which excluded a suspected rare autoimmune disorder of the central nervous system. Brain MRI was unremarkable, laboratory tests revealed elevated creatine kinase (CK) levels, and electromyography of all four limbs showed proximal myopathic involvement with mild signs of necrosis. Serological testing for myositis-specific antibodies was negative. The patient also underwent genetic counseling, which identified a heterozygous dynamin-2 (DNM2) variant (c.138A > G), considered potentially contributory but not etiopathogenic to the clinical phenotype. Muscle biopsy showed myofiber necrosis and regeneration with no inflammatory infiltrate. We concluded for seronegative immune-mediated necrotizing myopathy (IMNM).

Our goal was to identify the appropriate immunotherapeutic strategy. She started intravenous immunoglobulin therapy at a dose of 2 g/kg, followed by maintenance treatment with 1 g/kg monthly, with a good

clinical response.

In December 2024, she experienced wearing-off symptoms and required three cycles of plasma exchange with a transient, moderate benefit.

In March 2025, in an attempt to achieve disease stabilization, she started off-label efgartigimod, a neonatal Fc receptor antagonist, with subsequent improvement in ambulation and dysphagia.

EXPERIMENTAL THERAPIES

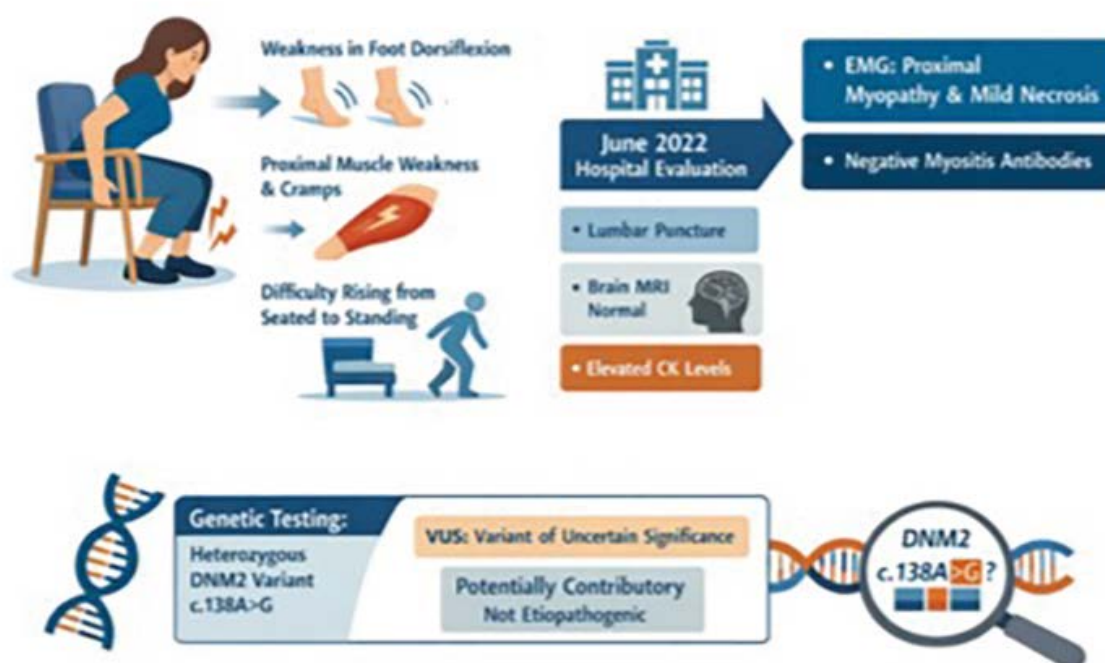
Abstract P064 - Cod. 143503

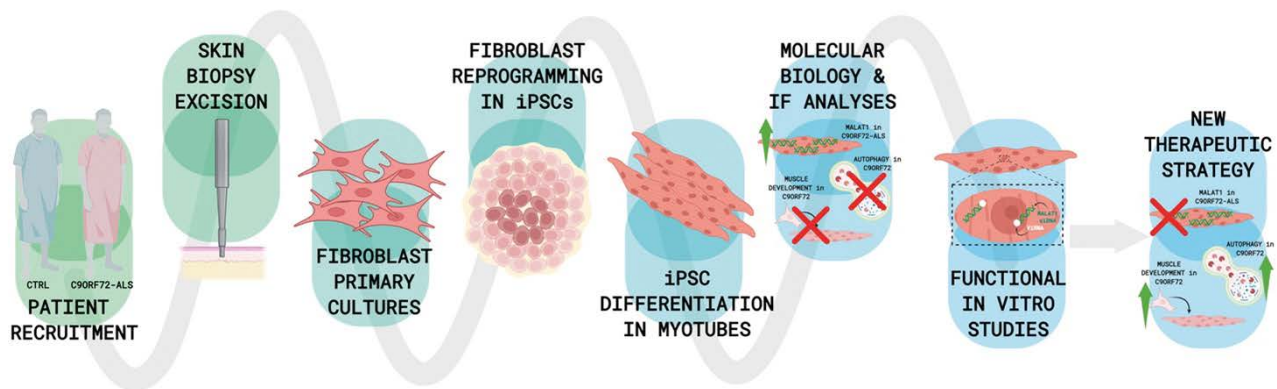
IPSC-DERIVED MUSCLE CELLS REVEAL A ROLE FOR MALAT1 LNCRNA IN AUTOPHAGY AND MYOGENESIS IN C9ORF72-ALS

Giagnorio E.¹, Bono N.², Malacarne C.¹, Cattaneo M.¹, Farinazzo G.¹, Pensato V.¹, Gellera C.¹, Bossolasco P.³, Ratti A.³, Salvi E.¹, Legati A.¹, Morris Verdone B.⁴, Ghezzi D.¹, Tedesco F.S.⁵, Pasinelli P.⁶, Candiani G.², Lauria Pinter G.¹, Bonanno S.¹, Marcuzzo S.¹

¹ Fondazione IRCCS Istituto Neurologico Carlo Besta, Milano, Italy, ² genT_LAB, Milano, Italy, ³ IRCCS Istituto Auxologico Italiano, Milano, Italy, ⁴ Johns Hopkins University, Baltimore, United States of America, ⁵ The Francis Crick Institute, London, United Kingdom, ⁶ Jefferson University, Philadelphia, United States of America

Amyotrophic lateral sclerosis (ALS) is traditionally viewed as a motor neuron-centric disorder, yet mounting evidence supports a paradigm shift in which skeletal muscle emerges as an active driver of disease





initiation and progression. The G4C2 repeat expansion in the C9orf72 gene, the most common genetic cause of ALS, profoundly alters RNA metabolism and autophagy, but its impact on human muscle development and homeostasis remains insufficiently defined.

This study investigated the molecular mechanisms underlying muscle dysfunction in C9orf72-ALS and identified potential long non-coding RNA (lncRNA)-based therapeutic targets using a patient-specific induced pluripotent stem cell (iPSC)-derived skeletal muscle model.

A robust and reproducible in vitro model of C9orf72-ALS myotubes was established from patient-derived induced pluripotent stem cells through a small-molecule differentiation protocol. iPSC-derived myotubes followed myogenic physiological differentiation, by expressing canonical differentiation markers, and they acquired contractile properties once mature. Crucially, patient-derived myotubes preserved key molecular hallmarks of C9orf72-ALS, including G4C2 repeat expansions, RNA foci, and dysregulation of autophagy-related genes, thereby faithfully recapitulating disease signatures in a ALS human muscle context. Transcriptomic profiling confirmed the muscle-specific identity of iPSC-derived myotubes and revealed significant dysregulation of MALAT1 lncRNA. MALAT1 was identified as a central regulator of muscle homeostasis and autophagy pathways, thus a critical driver of defective autophagy and impaired myogenic signaling in C9orf72-ALS context. Functional modulation of MALAT1 using a non-viral, nuclear-targeted siRNA delivery system successfully restored autophagy and myogenic gene expression.

Overall, this work positions skeletal muscle as a key and early site of pathology in C9orf72-ALS, provides a physiologically relevant human platform to dissect disease mechanisms, and highlights lncRNA-centered, nuclear-targeted interventions as promising therapeutic avenues for neuromuscular diseases.

NEUROBIOLOGY

Abstract P222 - Cod. 143402

EVALUATION OF IPSC-DERIVED SENSORY NEURONS AS A HUMAN IN VITRO MODEL FOR CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Naghshbandieh A.^{1,3}, D'Aprile C.¹, Donzelli E.¹, Rodriguez-Menendez V., Rigolio R.¹, Schachtele S.², Cavaletti G.¹, Scuteri A.¹
¹ Experimental Neurology Unit and Milan Center for Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Italy; ² FUJIFILM Cellular Dynamics, Inc., Madison, Wisconsin, USA; ³ PhD Program in Neuroscience, School of Medicine and Surgery, University of Milano-Bicocca, Italy

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common side effects of anticancer treatments, and it remains a major unmet clinical need, often leading to dose reduction or discontinuation of life-saving therapies. Despite decades of research, no effective preventive or therapeutic strategies are currently available, highlighting critical limitations in preclinical models used to study CIPN. Dorsal root ganglia (DRG) neurons represent the primary target of chemotherapy-induced neurotoxicity and have traditionally been studied using rodent DRG cultures. While these models provide valuable mechanistic insights, species-specific differences and genetic strain variability limit their translational predictability. Human-induced pluripotent stem cell (iPSC)-derived sensory neurons have emerged as a promising human-based model with strong genetic relevance, donor variability, and scalability for translational research.

Here, the suitability of FUJIFILM iCell® iPSC-derived sensory neurons as an in vitro model for CIPN was directly compared with primary rat DRG neuron cultures.

To obtain a comprehensive view of the system, we combined multiple experimental approaches, including immunofluorescence analysis, flow cytometry, neurite length measurements, and viability assessment after exposure to antineoplastic drugs. Our findings demonstrate that iPSC-derived sensory neurons exhibit robust neuronal identity and reproducible responses to neurotoxic stimuli, while retaining key phenotypic features of peripheral sensory neurons.

In summary, these results support the use of FUJIFILM iCell® Sensory Neurons, which are consistent with rat DRG data, confirming iPSC-derived sensory neurons as a valid human in vitro model for peripheral neuropathy and neurotoxicity testing.

NEUROBIOLOGY

Abstract P224 - Cod. 143282

FCRN BLOCKER EFGARTIGIMOD: UNIQUE FC FRAGMENT ALLOWING IGG REDUCTION WITHOUT REDUCING ALBUMIN OR INCREASING CHOLESTEROL

Amaroli A.^{*1}, Steeland S.¹, Ma G.², Crowley A.R.², Pannecoucke E.¹, Louagie E.¹, Podhorna J.¹, Heerlein K.¹, Heyndrickx L.¹, Rogiers I.¹, Van Santbergen J.¹, Bobkov V.¹, Balbino B.¹, Ward E.S.²

¹ argenx, Ghent, Belgium, ² Department Centre for Cancer Immunology, Faculty of Medicine, University of Southampton, Southampton, United Kingdom

The neonatal Fc receptor (FcRn) regulates both immunoglobulin G (IgG) and serum albumin homeostasis. While FcRn is an attractive target for antibody-mediated autoimmune disorders, albumin reductions were observed in previous studies with some FcRn blockers. Albumin maintains oncotic pressure and regulates fluid distribution, among other transporter functions, including maintaining lipid homeostasis.

Efgartigimod, an engineered human IgG1 Fc fragment, selectively binds to the IgG-binding site of FcRn with high affinity at acidic and neutral pH, preserving natural pH-dependent binding. Efgartigimod outcompetes endogenous IgG for binding to FcRn, thereby promoting lysosomal degradation of IgG, including pathogenic autoantibodies, without affecting other immunoglobulins or IgG production. Cellular/molecular analyses of multiple FcRn blockers have been performed to elucidate mechanisms leading to differential effects on albumin homeostasis.

Unlike some FcRn blockers in development, no reductions in albumin levels, increases in cholesterol, or notable occurrence of peripheral oedema were observed across efgartigimod studies, regardless of cyclic or weekly dosing, suggesting that differences in molecular interactions are responsible for the impact on albumin. Efgartigimod's Fc fragment binds to FcRn in the same orientation as natural IgG, preserving FcRn's fate and functioning in albumin recycling. Some FcRn blockers, however, reduce albumin levels through two potential mechanisms: decreasing FcRn expression and/or causing steric hindrance for albumin binding; limiting receptor availability. Transgenic mouse models further confirm these differential effects, recapitulating observed clinical findings.

Efgartigimod's unique molecular structure as an Fc fragment avoids clinical reduction of albumin levels, while effectively targeting IgG autoantibodies, making it a differentiated therapeutic option across dosing regimens.

NEUROBIOLOGY

Abstract P226 - Cod. 143436

INVESTIGATION OF PERIPHERAL NERVE INJURY USING [18F]DPA-714 PET IMAGING

Di Patrizi I.^{*2}, Camera M.¹, Roberta R.³, Emionite L.³, Riondato M.⁴, Losacco S.⁵, Chiesa S.⁶, Ghelardoni M.⁶, Dighero E.⁴, Schenone A.⁷, Marini C.⁵, Sambuceti G.⁵, Nobbio L.¹

¹ IRCCS Azienda Ospedaliera Metropolitana, U.O. Clinica Neurologica, ² IRCCS Azienda Ospedaliera Metropolitana, U.O. Radiologia, ³ IRCCS Azienda Ospedaliera Metropolitana, U.O. Animal Facility, Genova, Italy, ⁴ Università degli Studi di Genova, Dipartimento di Medicina Sperimentale, Genova, Italy, ⁵ Università degli Studi di Genova, Dipartimento di scienze della salute (DISSAL), Genova, Italy, ⁶ IRCCS Azienda Ospedaliera Metropolitana, U.O. Medicina Nucleare, Genova, Italy, ⁷ Università degli Studi di Genova, Dipartimento Neuroscienze, riabilitazione, oftalmologia, genetica e scienze materno-infantili (DINOEMI), Genova, Italy

Peripheral nerve injuries include a range of impairments that affect normal nerve structure and function, and lead to muscle denervation. Currently, there is no gold standard technique to monitor this phenomenon.

We tested a [18F]DPA-714 PET protocol on animal models of nerve injury. DPA-714 is a ligand for TSPO protein whose expression is relatively low in peripheral tissues during physiological conditions, and it increases with the activation of immune response. We evaluated changes in TSPO expression in mice at 7 and 14 days after the operation.

Mice examined 7 days after injury expressed high level of TSPO compared to contralateral control limb and sham mice, while TSPO expression was similar in mice examined 14 days after injury and sham mice. Western blot analysis highlighted an increased TSPO expression in crushed muscle of 7 and 14 days post-operation mice compared to control limbs and sham mice. Furthermore, immunofluorescence staining revealed a higher expression of CD68 (macrophage marker) in 7 days post-operation mice and co-localization of TSPO and CD68. Finally, we observed a clear muscle atrophy both in 7 and 14 days post-operation mice.

These findings suggest that [18F]DPA-714 PET could be used as a noninvasive biomarker to monitor the acute phase of nerve injury, when inflammation is high, whereas it appears to be less accurate in later phases, during which TSPO is detected by molecular analysis but not by imaging.

NEUROBIOLOGY

Abstract P228 - Cod. 143264

MODELLING CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY IN VITRO: A FOCUS ON ANGIOGENESIS-RELATED EVENTS

D'Aprile C.^{*}, Naghshbandieh A., Scuteri A., Carozzi V.A. Università degli Studi di Milano-Bicocca, Monza, Italy

Chemotherapy-induced peripheral neuropathy (CIPN) represents a common dose-limiting side effect of several anticancer drugs, including paclitaxel and cisplatin, with a major impact on patients' quality of life and with limited therapeutic options available. While sensory neuron damage is a well-established hallmark of CIPN, growing evidence suggests that non-neuronal components of the peripheral nervous system, such as the vascular compartment, may contribute to the disease

To explore the role of neurovascular interactions under physiological conditions and following chemotherapeutic exposure, advanced in vitro indirect co-culture models were established. Sensory dorsal root ganglion (DRG) neurons isolated from E15 Sprague Dawley rats were cultured alone or indirectly co-cultured with rat primary brain vascular endothelial cells (RPBECs).

A series of preliminary experiments were conducted to assess the feasibility of the experimental model. These experiments indicated improved survival of DRG neurons in co-culture compared to monocultures; however, distinct substrate requirements of the two cell populations restricted the system to indirect co-culture approaches. Subsequently, DRG neurons were exposed for 24 hours to paclitaxel (50nM) or cisplatin (2.5µM) and then maintained in indirect co-culture with endothelial cells. Under these conditions, the presence of endothelial cells appeared to influence neuronal responses to chemotherapeutic stress, suggesting a modulatory role driven by the vascular component. Conditioned media collected from monocultures and co-cultures, both under basal conditions and following chemotherapy exposure, will be analyzed using ELISA assays to evaluate the modulation of angiogenic factors.

These ongoing analyses will elucidate soluble mediators potentially involved in endothelial–neuronal communication during chemotherapy.

NEUROBIOLOGY

Abstract P230 - Cod. 143447

PHOTOACOUSTIC IMAGING ANALYSIS OF PMP22 TRANSGENIC RAT SCIATIC NERVE

Di Patrizi I.^{*1}, Astigiano S.², Dal Bello M.G.², Zaottini F.³, Malamal G.⁴, Jose J.⁵, Trochet P.⁵, Nobbio L.⁶

¹ IRCCS Azienda Ospedaliera Metropolitana, U.O. Radiologia, Genova, Italy, ² IRCCS Azienda Ospedaliera Metropolitana, U.O. Animal Facility, Genova, Italy, ³ Università degli Studi di Genova, Dipartimento di scienze della salute (DISSAL), Genova, Italy, ⁴ GE HealthCare, Bangalore, India, ⁵ FUJIFILM VisualSonics, Amsterdam, Netherlands, ⁶ IRCCS Azienda Ospedaliera Metropolitana, U.O. Clinica Neurologica, Genova, Jamaica

Photoacoustic (PA) imaging enables the identification of specific molecular structures based on the distinct optical absorption spectra of endogenous chromophores. Nanosecond laser pulses are delivered into biological tissues, where light is absorbed by chromophores and induces thermoelastic expansion which eventually generates ultrasound waves. Ultrasound and photoacoustic data are combined to produce images that provide both anatomical and molecular information.

We employed PA imaging to monitor the sciatic nerve in a rat model of Charcot–Marie–Tooth disease (CMT) type 1A neuropathy. We selected this animal model because previous studies have already demonstrated differences in the lipid and collagen composition in transgenic rats compared with wild-type (WT) littermates. Our aim was to establish a protocol for nerve visualization and to characterize its molecular composition, with a particular focus on lipids and collagen.

We initially performed PA imaging on excised sciatic nerves, and subsequently extended the study to in vivo experiments. We implement-

ed SPAX analysis which enables multiple-wavelength acquisition, and automatically identify the absorption spectra that best represent tissue components. We observed an increase in collagen content in CMT nerves compared to WT, in agreement with our previous histological findings. However we could not detect the expected difference in lipid content.

Even though we still need to work on the identification of the optimal wavelengths for collagen and lipid detection, photoacoustic imaging has proven to be a valuable technique due to its rapid acquisition and non-invasive nature.

NEUROBIOLOGY

Abstract P232 - Cod. 143068

THE EFFECT OF ANTIBIOTIC-INDUCED DYSBIOSIS ON PERIPHERAL NERVE REPAIR

Pellegrino D.^{*1}, El Soury M.¹, Farzin S.¹, Elmelegy A.A.¹, Muratori L.¹, Calabrò S.³, Ferrocino I.², Ferrero G.¹, Camandona A.¹, Haastert--Talini K.⁴, Cescon M.³, Gambarotta G.¹, Ronchi G.¹

¹ Department of Clinical and Biological Sciences & Neuroscience Institute Cavalieri Ottolenghi (NICO), University of Torino, Orbassano, (Torino), Italy, ² Department of Scienze Agrarie, Forestali e Alimentari – DISAFA, University of Torino, Grugliasco, Torino, Italy, ³ Department of Molecular Medicine, University of Padova, Padova, Italy, ⁴ Institute of Neuroanatomy and Cell Biology, Hannover Medical School, Carl-Neuberg-Str. 1, Hannover, Germany

Human gut microbiota is a dynamic and complex community of microorganisms, including bacteria, fungi, protozoa and viruses, that contributes to tissue homeostasis through multiple physiological functions. Beyond its role in gastrointestinal health, the gut microbiota influences barrier integrity, metabolism, hematopoiesis and inflammation, leading to its recognition as a “vital organ”. Recently, our laboratory identified a novel connection between the gut microbiota and the peripheral nervous system (PNS).

To investigate the impact of microbiota composition on peripheral nerve regeneration, we administered to mice a cocktail of antibiotics (vancomycin 0.25 mg/mL, ampicillin 0.5 mg/mL, metronidazole 0.5 mg/mL) via drinking water.

Animals were divided into four groups: Group 1 (treated before and after surgery), Group 2 (treated only before surgery), Group 3 (treated only after surgery) and Group 4 (untreated controls). Mice underwent peripheral nerve injury (transection or crush) and tissues were collected at 2, 7, or 28 days. Functional recovery was assessed using the grasping test.

Antibiotic treatment did not cause weight loss or evident behavioral alterations. Microbiota analysis confirmed that antibiotic treatment induced dysbiosis, with the extent and nature of the disruption varying according to treatment duration. Functionally, mice receiving antibiotics prior to median nerve injury showed reduced grip strength in the injured forelimb up to day 10 post-injury compared to untreated animals, with comparable recovery across groups by day 28.

These findings indicate that microbiota depletion induces transient functional alterations in the PNS. Further analyses are ongoing to elucidate the underlying mechanisms.

NEUROBIOLOGY

Abstract P234 - Cod. 143259

THE PIVOTAL ROLE OF NCX INHIBITORS IN NEUROPROTECTION AGAINST OXALIPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

Di Girolamo S.^{*1}, Invernizzi C.¹, Kraus M.², Alberti P.³¹ University of Milano-Bicocca, Monza, Italy, ² S.C. Neuroscienze, Istituto Zooprofilattico Sperimentale del Piemonte Liguria e Valle D'Aosta, Turin, Italy, ³ Department of Neurology, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy

Oxaliplatin (OHP) is a cornerstone in colorectal cancer treatment but its clinical use is limited by OHP-induced peripheral neurotoxicity (OIPN), which includes an acute and a chronic form. Acute OIPN manifests early as transient axonal hyperexcitability caused by functional alterations of voltage-gated sodium channels (NaV). Chronic OIPN presents as a persistent sensory neuronopathy characterized by axonal damage (AxD). These two conditions may be mechanistically linked: NaV dysfunction increases intracellular Na⁺ levels, potentially activating the Sodium-Calcium Exchanger (NCX) in reverse-mode. This results in Ca²⁺ influx, leading to toxic accumulation and axonal degeneration.

The present study investigated the role of NCX in AxD using an in vitro OIPN model. Dorsal root ganglia primary neuronal cultures (male C57BL/6 mice) were analyzed using the Nanolive CX-A 3D holotomographic microscope for live-cell imaging. We tested potential neuroprotective strategies, including SEA0400, a potent NCX inhibitor, and siRNAs targeting NCX2, the most highly expressed neuronal isoform. Exposure to OHP (7.5–25 μM, 48h) induced significant neurotoxicity, evidenced by neurite fragmentation and reduced cell viability, preceded by autophagic stress and necroptosis in a dose/time-dependent manner. SEA0400 (1 μM, 3h pre-treatment) effectively mitigated these pathological changes. Moreover, OHP induced alterations were more strongly prevented by downregulating NCX2 expression via siRNAs (5nM, 24h pre treatment).

Overall, our findings show that OIPN related AxD can be prevented by targeting NCX family—particularly NCX2—highlighting promising therapeutic avenues for AxD prevention. Notably, this mechanism may be relevant beyond OIPN, as axonal hyperexcitability and NCX mediated Ca²⁺ toxicity have also been implicated in genetic, inflammatory, and metabolic neuropathies.

OTHER MOTOR NEURON DISORDERS

Abstract P248 - Cod. 143463

DERMAL FIBROBLASTS FROM AMYOTROPHIC LATERAL SCLEROSIS PATIENTS AS A USEFUL TOOL TO STUDY AUTOPHAGY-LYSOSOME PATHWAY ALTERATIONS

Vietri G.^{*1}, Gruosso F.¹, Goglia M.¹, Frezza E.¹, Greco G.¹, Boffa L.¹, Centonze D.¹, Rocchi C.¹, Ciaiola F.², Spalloni A.², Caldarola M.², De Mori R.³, Massa R.¹, Longone P.²¹ Department of Systems Medicine, University of Rome Tor Vergata, Rome,Italy, ² Molecular Neurobiology Unit, Experimental Neurology, Fondazione Santa Lucia, Rome, Italy, ³ Stem Cell Facility, Fondazione Santa Lucia, Rome, Italy

Amyotrophic lateral sclerosis (ALS) is increasingly recognized as a multisystemic disorder. Increasing evidence, among the many systems involved, points to dysfunction of the autophagy-lysosome pathway (ALP) as a key pathway across sporadic and genetic ALS. In this context, patient-derived cellular models may enable patient-specific profiling and quantitative approaches to patient stratification. We investigated whether primary dermal fibroblasts from ALS patients reflect ALP-related cellular and molecular alterations observed in the disease.

In this monocentric observational pilot study, patients (mild-to-moderate stages) and matched healthy controls were enrolled, with exclusion of major metabolic comorbidities. Skin biopsies were obtained and primary fibroblast cultures were established. Proliferation rate was assessed and, in order to study ALP further, ALP-related markers were evaluated using immunoblotting with antibodies against autophagy-related markers. Qualitative protein distribution was assessed through immunofluorescence for autophagy markers.

Of nine biopsies, five lines produced a complete colony, four cultures showed a reduced clonal production. The ALS cohort included sporadic and genetic forms with heterogenous genotype. Compared with matched healthy controls, ALS fibroblasts showed a slower growth rate, with significantly reduced cell numbers at 24 hours and 96 hours. Preliminary western blot and immunofluorescence data confirmed an altered autophagy pathway.

Patient-derived dermal fibroblasts in ALS display convergent abnormalities across proliferation, autophagic pathways, and lysosomal organization, supporting an early peripheral ALP defect compatible with a multisystemic model of ALS. Despite the small sample size and reduced culture survival, the agreement across independent assays suggest that fibroblast-based multi-marker assays may capture biologically meaningful heterogeneity useful for patient stratification.

OTHER MOTOR NEURON DISORDERS

Abstract P250 - Cod. 143501

ELEVATED PLASMA P-TAU181 IN AMYOTROPHIC LATERAL SCLEROSIS IS LINKED WITH SLOWER DISEASE PROGRESSION

Goglia M.^{*1}, Frezza E.¹, Greco G.¹, Gruosso F.¹, Vietri G.¹, Nuccetelli M.², Boffa L.¹, Centonze D.³, Massa R.¹¹ Neuromuscular Diseases Unit, Department of Systems Medicine, Tor Vergata University of Rome, Rome, Italy, ² Department of Clinical Biochemistry and Molecular Biology, University of Rome "Tor Vergata", Rome, Italy, ³ Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy

Plasma phosphorylated tau181 (p-tau181) has emerged as a potential dynamic biomarker of axonal-motor neuron and muscle damage in amyotrophic lateral sclerosis (ALS). Recently, p-tau181 levels have also been described in myotonic dystrophy type 1 (DM1) as a promising novel biomarker of brain and skeletal muscle injury.

The aim of this study is to evaluate plasma p-tau181 in ALS versus pathologic (DM1) and healthy controls, and its prognostic value for functional decline in ALS. Plasma p-tau181 levels were detected with ELISA immunoassay. ALS-functional rating scale revised (ALS-FRS-R) was calculated for ALS patients. MRC sum score was calculated both for ALS and DM1 patients.

We enrolled 18 ALS patients (11 male; 7 female), 23 DM1 patients (14 male; 9 female; 12 MIRS 3; 11 MIRS 4) and 18 healthy controls. Both ALS and DM1 showed elevated plasma p-tau181 vs controls ($p \leq 0.002$), with no difference between diseases ($p = 0.197$). Adjusting for MRC sum score, significant higher values in ALS vs. DM1 were found ($F = 4.62$, $p = 0.038$, $d = 0.70$). In a longitudinal linear mixed model, higher baseline p-tau181 predicted slower functional decline in ALS ($B = 0.068$, $p < .001$).

Muscle wasting may contribute to p-tau181 elevation in both ALS and DM1. However, after MRC adjustment, p-tau181 was significantly higher in ALS, likely reflecting the more aggressive nature of this disease. However, higher baseline p tau181 in ALS was associated with a slower functional decline, typical of prevalent lower motor neuron phenotype, possibly suggesting a preferential peripheral origin of this biomarker.

OTHER MOTOR NEURON DISORDERS

Abstract P252 - Cod. 143515

TDP-43 PATHOLOGY INDUCES CD8 T CELL

ACTIVATION THROUGH CRYPTIC EPITOPE RECOGNITION

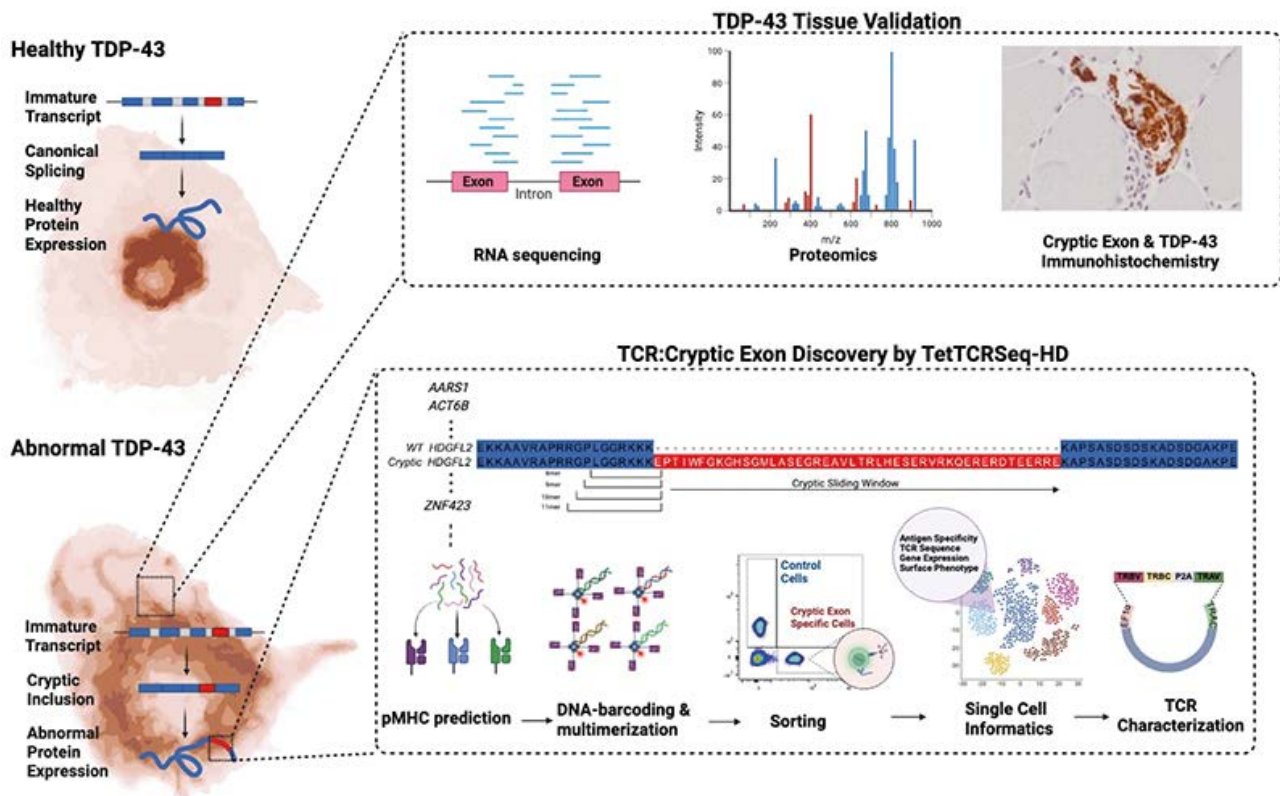
Zanovello M.^{*1}, Chizari S.², Kong S.², Soraru G.³, Jiang N.², Fratta P.¹

¹ UCL, London, United Kingdom, ² University of Pennsylvania, Philadelphia, PA, United States of America, ³ Università di Padova, Padova, Italy

Aggregation and nuclear depletion of the RNA binding protein TDP-43 are crucial pathological features of amyotrophic lateral sclerosis (ALS), inclusion body myositis (IBM) and multisystem proteinopathy (MSP). The loss of TDP-43 nuclear function results in the aberrant inclusion of cryptic exons in mRNA transcripts, leading to the expression of de novo proteins. Clonally expanded and highly differentiated CD8+ T cells have been observed in individuals with TDP-43 proteinopathies. However, the target antigens mediating T cell activation have remained elusive.

Here, we investigate whether the de novo proteins induced by aberrant cryptic splicing due to TDP-43 nuclear loss can act as neo-antigens.

By combining RNA-sequencing, immunohistochemistry and proteomics, we detect the HDGFL2 cryptic peptide and multiple other TDP-43 cryptic exons in IBM skeletal muscle, where their presence correlates with enrichment of T cells and MHC-I antigen presentation. Furthermore, using TetTCR-SeqHD, a high-throughput and multidimensional single T cell profiling approach, we identify epitopes from HDGFL2 and IGLON5 cryptic peptides which are recognized by clonally expanded and functionally differentiated CD8+ T cells in ALS and IBM patients. Finally, we demonstrate that T cells engineered to



express the identified TCRs can activate in response to the cryptic peptides and are able to kill TDP-43 deficient cells.

This work identifies for the first time specific T cell antigens in TDP-43 proteinopathies, directly linking adaptive immune response to TDP-43 pathology.

OTHER MOTOR NEURON DISORDERS

Abstract P254 - Cod. 142977

“TIME WILL TELL”: AN ATYPICAL PRESENTATION OF A HSPB1-RELATED DISORDER

Urbano G.*, Gadaleta G., Maccarrone G., Boschi S., Leopizzi E., Rolle E., Vercelli L., Mongini T.

1. Neuromuscular Unit, University of Turin, Department of Neurosciences “Rita Levi Montalcini”, Torino, Italy

HSPB1 encodes heat shock protein 27 (HSP27), a small HSP involved in cellular stress response and cytoskeletal stability in muscles and peripheral nerves. HSPB1 mutations are usually associated with CMT2F and distal hereditary motor neuropathies.

To provide a longitudinal description of an HSPB1 case with atypical features.

We describe the case of a 56-year-old man first evaluated in 2010 for lower-limb cramps and persistent hyperckemia (x 4-5 ULN). Neurological examination revealed proximal lower-limb weakness, hypoactive deep tendon reflexes, a waddling gait, and difficulty climbing stairs. Medical history was notable for type 2 diabetes, in absence of other neurological features. A right quadriceps muscle biopsy showed nonspecific neurogenic changes, marked increased lipid content, and reduced carnitine enzymatic activity, leading to a diagnosis of lipid storage myopathy and initiation of supplementary therapy with partial benefit on disease progression. In the subsequent years, the patient developed progressive distal hypotrophy and weakness, steppage gait, and recurrent falls. An electromyography documented a severe axonal motor neuropathy with overlapping polyneuropathic sensory involvement, while lower-limb muscle MRI revealed extensive neurogenic fibrofatty replacement. Based on these findings, a next-generation sequencing targeting both myopathy- and neuropathy-related genes was performed, and a heterozygous pathogenic variant c.407G > T (p. Arg136Leu) in HSPB1 was identified and deemed compatible with the clinical picture.

Although myopathic features have already been described in these forms, our case highlights how atypical findings and asynchronous symptom evolution can delay a correct diagnosis. Longitudinal re-evaluations of neurophysiological, radiological, clinical, and extensive genetic panels are key to disentangling complex phenotypes.

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