EXECUTIVE SUMMARY

WORKSHOP

CONTRACTURES IN SMA:
FROM SCIENTIFIC INSIGHTS TO THERAPEUTIC TARGETS

INTERNATIONAL SCIENTIFIC CONGRESS ON SMA, BUDAPEST CONGRESS CENTRE

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Organized by

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TABLE OF CONTENTS

OPENING REMARKS AND SETTING THE DIRECTION OF THE WORKSHOP

- Contractures represent a largely “unseen” yet clinically significant complication in neuromuscular diseases. Despite their substantial impact on patient function and quality of life, they have historically been under-recognised and insufficiently studied.

- Greater conceptual and terminological clarity is needed, as the term “contracture” has often been used interchangeably for neuromotor problems caused by spasticity or dystonia. Within the neuromuscular field, it is important to distinguish structural contractures, referring to alterations in the physical and morphological properties of muscle and surrounding tissues, from movement disorders such as spasticity or dystonia. This distinction is critical for both research and clinical management.

- It is possible that the underlying mechanisms of contractures may vary across different neuromuscular conditions. Potential mechanisms may include imbalances in muscle forces, leading to uneven mechanical pull, as well as intrinsic changes within muscle tissue. Further research is required to elucidate these mechanisms and determine disease-specific pathways.

- Despite over three decades of clinical use, the role of stretching in the prevention and management of contractures remains inconclusive. Persistent uncertainties, particularly regarding its long-term efficacy and the balance between potential benefits and associated discomfort or pain, highlight the need for more robust and methodologically rigorous studies.

TOM CRAWFORD

Professor of Neurology, Johns Hopkins School of Medicine Faculty, USA

CONTRACTURES IN SMA: AN URGENT UNMET NEED FOR PATIENTS

- FundAME, the Spanish SMA patient organization, recognised the relevance of contractures for people living with spinal muscular atrophy and is gathering evidence on their impact through the Spanish SMA Registry, RegistrAME with data on more than 375 individuals, 44% of whom reported having contractures. According to some studies, up to 80% of the people living with SMA will develop contractures at some point.

- Contractures restrict essential activities like oral and body hygiene, wearing shoes, standing, and self-care. In addition to limiting functional capacity, they are also associated with pain.

- Current management approaches pose challenges to treatment adherence. Standard of care recommendations include the overnight use of orthoses, daily stretching routines, and the use of standing frames for a minimum of 60 minutes per day up to 7 days a week.

- Contractures have a significant impact on function, quality of life, care and limit the full therapeutic potential of treatments. Research is needed to better prevent, effectively manage and revert contractures and investment is urgently needed to address these patient needs.

MENCÍA DE LEMUS

CEO and Patient expert, FundAME, Spain

CELLULAR AND ULTRASTRUCTURAL BASES OF CONTRACTURES: CURRENT KNOWLEDGE, OPEN QUESTIONS AND IMPLICATIONS FOR SMA

- Movement is a complex process that involves the coordinated interaction of multiple tissues and cell types. To understand contractures, it is necessary to adopt a comprehensive perspective and examine the different components of the motor system. A basic science overview of the cellular and ultrastructural basis of contractures in spinal muscular atrophy is presented.

- In murine models of SMA, alterations are observed from birth. These alterations occur independently of motor neuron degeneration, suggesting the presence of primary muscle-specific defects.

- Treatments that restore SMN levels prevent the loss of motor neurons and largely reverse muscle atrophy and fibre size. However, some dysfunction remains, meaning that current treatments cannot fully restore muscle function, which is driving further research into these cellular structures.

- It is argued that these muscle alterations alone do not fully explain joint fixation. Contractures should instead be understood as a mechanical remodelling phenotype involving muscle, tendon, bone, the neuromuscular junction, and both motor and sensory innervation.

- To support hypothesis generation, the presentation draws comparisons between SMA and other conditions associated with contractures, including COL6-related congenital muscular dystrophy and distal arthrogryposis type 5.

OLGA TAPIA

Dept. Basic Medical Sciences & Institute of Biomedical Technologies, University of La Laguna, Spain

FROM IMAGING TO TISSUE ANALYSIS: WHAT DO WE KNOW ABOUT MUSCLE FIBROSIS, STIFFNESS AND CONTRACTURES IN SMA

- Imaging and tissue analysis in SMA are reviewed, starting from MRI in neuromuscular diseases and explaining how muscle inflammation produces increased water content (oedema) in the context of active denervation.

- When chronic changes appear, there is a progressive atrophy and muscle fibre loss leads to fatty and fibrotic replacement in a very particular way called reticular pattern. In SMA, muscle involvement is not random but follows a stereotyped pattern because muscles progress at different time.

- Fat replacement is common across muscular dystrophies, metabolic diseases, neurogenic disorders (including SMA, ALS, neuropathies), and inflammatory myopathies, making MRI a broadly useful but non-specific tool.

- There is a correlation between fat and stiffness. To understand what makes tissue stiffer, the group analyses SMA and ALS muscle biopsies. Findings show that over 80% of dysregulated muscle pathways are shared between SMA and ALS.

- The proposed working model is that denervation causes weakness, while adipogenesis and fibrosis progressively stiffen the muscle; a weak and stiff muscle tends to shorten, which may promote contracture formation, although the contribution and structural changes of other tissues such as tendon and joint capsule remain largely unknown.

JORDI DÍAZ-MANERA

The John Walton Muscular Dystrophy Research Center, Translational & Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK)

CLINICAL ASSESSMENT AND MANAGEMENT OF CONTRACTURES: KEY PARAMETERS, MEASUREMENT STANDARDS, AND EVIDENCE GAPS

- The distinctions between contractures, tightness, and flexibility must be clearly defined to ensure effective communication. Without alignment on these definitions, there is a risk of misunderstanding the intended targets among basic scientists, clinicians, and biomechanists. It is essential for all parties to establish consensus regarding terminology.

- Management goals are framed as improving function, preventing deformity, and reducing pain, with caution that lengthening a muscle or tendon does not necessarily improve strength (so careful consideration must be given to the use of surgical techniques) and can worsen function if biomechanics are not respected (because if a change in biomechanics is aimed, you need increased muscle strength to compensate for that).

- There is large measurement variability in how contractures and stiffness are assessed, which hampers both clinical decision-making and clinical trials.

- Available tools for managing contractures in SMA are limited mainly to stretching and bracing.

- Bracing might not stop contractures, but it helps maintain muscle extensibility. It's important to begin early while tissue remains flexible.

TINA DUONG

PhD (Department of Neurology, Stanford University, USA)

CLINICAL ASSESSMENT AND MANAGEMENT OF CONTRACTURES: KEY PARAMETERS, MEASUREMENT STANDARDS, AND EVIDENCE GAPS

- Stretching has a function in increasing the ability to activate muscle contraction, which is a different approach from treating a fixed contracture. Reviews of stretching studies find little effect of stretching on joint range of motion, In contrast with patient reports of feeling better, walking better, and reduced stiffness after stretching or massage, proposing that changes in pain perception, compliance, or vascular function could explain this discrepancy.

- There is a coexistence of contractures and hypermobility in SMA that can be functionally compensatory in patients with weak muscles, so interventions must always be judged against their impact on function.

- It was showed an increase in strength after the administration of disease-modifying treatment without any difference in the muscle imbalance. Then, strength training of extensors, if possible, and more support of flexors could complement disease-modifying treatments in order to increase muscle imbalance and improved contractures in treated people with SMA II or SMA III.

- The proposal of setting up a new meeting with basic scientists, biomechanists, physiotherapists, and doctors to speak together to move forward the topic of contractures in SMA.

TINA DUONG

PhD (Department of Neurology, Stanford University, USA)

CLOSING REMARKS

- SMA is now an excellent “clean” model to study contractures thanks to new molecular and imaging tools and changing phenotypes under early treatment.
- New treatment paradigms as anti-fibrotic and other novel treatments should be studied.
- A fundamental investigation examining how muscles adjust their contractile components in response to connective tissue limitations, utilizing SMA as a representative model for broader muscle biology, should be conducted

TOM CRAWFORD

Professor of Neurology, Johns Hopkins School of Medicine Faculty, USA

ABOUT FUNDAME

FundAME, a Spinal Muscular Atrophy (SMA) Patient Organization, was established in 2005 with the following objectives:

- To advance and disseminate scientific and clinical knowledge on SMA
- To support high-quality research initiatives aimed at achieving a definitive cure
- To advocate for equitable access to evidence-based treatment for the SMA community

FundAME is committed to improving the quality of life of individuals living with SMA and their families through a rigorous, evidence-based approach.
FundAME focuses on fostering innovative research in close collaboration with the scientific community, strengthening advocacy to ensure timely access to clinically validated therapies and high standards of care.
FundAME promotes the dissemination of specialized, up-to-date knowledge among researchers, healthcare professionals, patients, and caregivers.

OUR VISION

FundAME envisions a future in which Spinal Muscular Atrophy is curable, and all individuals affected by SMA—including families and caregivers— have access to the treatment, care, and resources necessary to lead independent, fulfilling lives and participate fully in society.

FundAME

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