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Founders: Giovanni Nigro and Lucia Ines Comi

Three-monthly

G. CONTE ACADEMY - NAPOLI

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Acute hospitalisation may be required to support patients with Neuromuscular disorders (NMDs) mainly experiencing respiratory complications, swallowing difficulties, heart failure, urgent surgical procedures. As NMDs may need specific treatments, they should be ideally managed in specialized hospitals. Nevertheless, if urgent treatment is required, patients with NMD should be managed at the closest hospital site, which may not be a specialized centre where local emergency physicians have the adequate experience to manage these patients. Although NMDs are a group of conditions that can differ in terms of disease onset, progression, severity and involvement of other systems, many recommendations are transversal and apply to the most frequent NMDs. Emergency Cards (EC), which report the most common recommendations on respiratory and cardiac issues and provide indications for drugs/treatments to be used with caution, are actively used in some countries by patients with NMDs. In Italy, there is no consensus on the use of any EC, and a minority of patients adopt it regularly in case of emergency. In April 2022, 50 participants from different centres in Italy met in Milan, Italy, to agree on a minimum set of recommendations for urgent care management which can be extended to the vast majority of NMDs. The aim of the workshop was to agree on the most relevant information and recommendations regarding the main topics related to emergency care of patients with NMD in order to produce specific ECs for the 13 most frequent NMDs.

Key words: neuromuscular diseases, respiratory complications, cardiac complications, swallowing difficulties, anaesthesia, emergency card, critical care.

Introduction

Neuromuscular disorders (NMDs) are a heterogeneous group of diseases affecting the function of motor neurons, peripheral nerve, neuromuscular junction, or skeletal muscles. When muscle weakness involves respiratory, bulbar and/or cardiac muscles, NMD may lead to respiratory, swallowing and/or cardiac complications [1-12]. Acute hospitalization may be required to support patients with NMDs, who can experience a range of common affections or conditions (e.g., respiratory infections, heart failure, urgent surgical procedures, bone fractures, labour and delivery) [2,4,5,7,13-18]. As these patients may need specific treatments, such as non-invasive ventilation (NIV), assisted cough [4,5,7,12,14-16,19-30], and dedicated extubation strategies [31,32], they should be ideally managed in specialized hospitals that have the appropriate technical tools and human resources [33,34]. Nevertheless, if urgent treatments are required, patients should be managed at the closest hospital site, which may not be one of the specialized centres for NMD [34]. Since NMDs are rare diseases and are an uncommon cause of emergency department and ICU admissions [33], local emergency physicians and intensivists may not have the adequate experience to manage these patients [5,34].

Although NMDs are a group of conditions that may differ in terms of disease onset, progression, severity and involvement of other systems, many recommendations can apply to the vast majority of NMDs. In particular, they all may require a similar management in case of acute respiratory, cardiac and swallowing complications and may require a similar perioperative management.

The introduction of an emergency card (EC) for patients with NMDs has been identified as a possible solution to improve local acute care [5,34,35]. The EC is intended as a pocket guide for Emergency Department physicians, to provide an overview of key issues related to the emer-

gency management of patients with NMDs [34]. Patients should take it with them when they seek acute care. While EC are already actively used in some countries by patients with NMDs there is no consensus and wide use in Italy for any of the most common diseases.

To fill this gap, 50 participants from 39 Italian tertiary centres met in Milan, Italy, to agree on a minimum set of recommendations for urgent care management which can be extended to the vast majority of NMDs. The aim of the workshop was to agree on the most relevant informations and recommendations regarding the main topics related to urgent care of the vast majority of NMDs in order to produce an EC for the 13 most frequent NMDs.

An informal consensus technique was used that involved group discussions moderated by senior chairpersons. Any information or suggestion of care and management was presented and voted by the panel of experts during a plenary roundtable and two web-based surveys.

Methods

In January 2020, the UILDM (Italian Muscular Dystrophy Association) Medical Scientific Committee (UILDM-MSC) discussed on the current emergency care issues for patients with NMDs. It became immediately clear that the wide variation of medical care received by NMDs patients in the emergency setting likely increases the variability of clinical outcomes. Thus, the UILDM-MSC nominated an eight-member Core Committee (CC) with the aim of organizing a Consensus Conference that formulates the EC for the most frequent NMDs. The CC consisted of six physicians (4 neurologists, 1 pulmonologist, 1 anesthesiologist/intensivist), one physiotherapist and one patient representative from UILDM. This CC appointed two chairmen (FRac and ClB). All committee members participated on a voluntary basis, with no compensation. During the planning stages of Consensus Conference, the co-Chairs frequently communicated with the CC. It was decided to focus on the emergency management of the following NMDs: Spinal muscular atrophy type 1, type 2 and type 3, Charcot-Marie-Tooth disease, Duchenne Muscular dystrophy, Becker Muscular dystrophy, Myotonic dystrophy type 1, Limb girdle muscular dystrophy, Facioscapulohumeral muscular dystrophy, Congenital muscular dystrophy, Congenital myopathies, Mitochondrial myopathies, Glycogen storage myopathies. The CC selected seven main domains which are typically associated with clinical problems and require urgent care: i) acute respiratory failure; ii) chocking due to swallowing difficulties; iii); cardiac complications; iv) anaesthetic precautions and perioperative management; v) falls and fractures; vi) acute constipation due to bowel dysfunction; vii) other issues.

The format of EC was drafted to provide a readily accessible compilation of main topics related to the emergency care of these patients (Tab. I).

The most relevant literature in the field was identified by querying PubMed (www.pubmed.gov) from January 1991 to December 2021, including only human studies. We used the search terms “neuromuscular diseases”, “spinal muscular atrophy”, “Charcot-Marie-Tooth disease”, “myopathy”, “muscular dystrophy”, cross-referenced with the term “respiratory complications”, “cardiac complications”, “swallowing difficulties”, “anesthesia” and “fractures”. We identified 352 out of 10.000 articles as relevant to the document.

Table I. Standard format chosen for the compilation of the emergency card.

EMERGENCY CARD for patients with _____	
Name_____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____ as soon as possible on: _____	
Main topics	**Most relevant informations and recommendations related to the emergency care**
Acute respiratory insufficiency	Key issues and management
Chocking due to swallowing difficulties	Key issues and management
Acute cardiac Complications	Key issues and management
Anaesthetic precautions And perioperative management	Key issues and management
Falls and fractures	Key issues and management
Acute constipation due to bowel dysfunction	Key issues and management
Other issues	Key issues and management

The CC decided to focus on a minimum set of common recommendations for different NMDs and drafted consensus statements on each area of care based on the literature results and personal experience. The effort was to select the most important consensus-based recommendations acceptable to the panel and amenable to application by physicians not specialized in NMDs in the Emergency Departments.

The Co-Chairs and CC worked together to establish an Italian consensus working group (CWG), sharing the responsibility for nominating and approving participants. The panel selection was based on a) clinical and scientific experience in NMDs; b) involvement in acute care management of NMDs patients; c) the need to have different health-care professionals who could provide knowledge and experience in the different domains described above; d) geographic diversity; and e) ability to commit time to the CC process. Ultimately, the panel consisted of 49 clinically-active physicians, involved in acute management of paediatric and adult neuromuscular patients (24 neurologists, 5 pulmonologists, 7 anesthesiologists and intensivists, 3 emergency medicine specialists, 3 pediatricians, 3 orthopedics, 2 cardiologists, 1 physiatrist, 1 physiotherapist) and one patient representative. The panelists came from different Regions of Italy. Representatives from the medical groups such as the Italian Muscle Association (AIM, Associazione Italiana Miologia), the Italian Pulmonology Association (AIPO, Associazione Italiana Pneumologi Ospedalieri), the Italian Pediatric Respiratory Association (SIMRI, Società Italiana Medicina Respiratoria Infantile), the Italian Neonatal and Pediatric Reanimation Society (SARNePI, Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana), the Italian Emergency Care Society (SIMEU, Società Italiana della medicina di emergenza-urgenza), the Italian Pediatric Emergency Care Society (SIMEUP, Società Italiana di Medicina di Emergenza e Urgenza Pediatrica) actively partecipate to the CC.

Starting three months before the meeting, the consensus working group (CWG) completed a web-based survey. A set of 45 close-ended questions was constructed for each of the seven main topics. Panellists were encouraged to limit their responses to the respective areas of expertise. In case of disagreement with the statement proposed by the application, they were encouraged to give feedback in order to clarify the reasons for their dissent. Consensus was reached with a percentage of votes in favour greater than 85%. Points for which consensus was not reached were reviewed by the leadership team based on feedback from the panel. All responses were summarized and presented by the Co-Chairs to panel members during the in-person Consensus Conference meeting. The meeting took place on 13th April 2022 in Milan. The entire group discussed all recommendations and voted for the revised version, using the same 85% criterion. The Co-Chairs ensured that every one of the working group had the opportunity to present and debate their views and ensured that discussions were open and constructive.

At the end of the meeting, the Co-Chairs revised the recommendations for which consensus was not reached and sent a second web-based survey to obtain an additional round of votes to reach consensus on the revised statements. All the activities were completed between December 2020 and May 2022.

Results

Consensus, that was reached on keys issues and management of acute respiratory failure, chocking, cardiac complications, anaesthesia, fractures and acute constipation is summarized in four tables (Tabs. II-V) and 37 statements (Tab. VI). Subsequently, the CWG defined 13 ECs, one for each disease, all sharing the same structure but with disease-related specifities. These cards are presented as on-line support information.

The general considerations for the most frequent clinical conditions potentially requiring urgent care and the recommendations and management strategies are outlined in the following paragraphs.

Key issues and management of acute respiratory failure

The probability of occurrence of respiratory complications is different in NMDs depending on the disease and age (Tab. II) [14,16,36-38] and may be the main cause of death [13,36,39,40]. The weakness of inspiratory muscles affects the ability to ventilate and leads to alveolar hypoventilation and hypercapnia. In addition, the involvement of expiratory muscles impairs the ability to clear airway secretions, inducing mucus plugging and hypoxemia [14,38,39,41]. The presence of severe scoliosis, which develops mainly in patients with NMDs, who lose independent ambulation before adulthood, further increases the risk of respiratory complications [14,42-44].

The use of Non Invasive Ventilation (NIV) associated with cough assist device, reduces the risk of alveolar hypoventilation and airway secretion retention, decreasing the number of hospital admissions, intubation, and tracheostomy [14,19-29,45,46]. Acute intercurrent events can lead to respiratory exacerbation and acute respiratory failure (RF) [14,41]. Respiratory tract infections are the most common cause of hospitalization for patients with NMDs , triggering over 90% of episodes of acute RF [40]. In case of airway infections, the weakness of the expiratory muscles, especially when associated with weakness of the inspiratory muscles, causes cough deficit with accumulation of bronchial secretions and increased work of breath-

Table II. Respiratory complications in neuromuscular disorders.

Disorder	Respiratory complications
SMA type 1	Always present (early onset; frequent exacerbation)
SMA type 2	Frequent (progressive)
SMA type 3	Occasional (progressive)
CMT	Occasional in some subtypes (progressive)
DMD	Always present in adulthood (progressive; frequent exacerbation)
BMD	Occasional (progressive)
DM1	Frequent (progressive; central sleep apnea is also reported)
LGMD	Frequent in some subtypes (LGMD1, LGMD2C/D/E/F)
FSHD	Occasional (progressive)
CMD	Frequent in some subtypes (Ullrich's CMD, LAMA 2 deficient CMD)
CM	Frequent in some subtypes (nemaline, myofibrillary and centro-nuclear CM)
Mitochondrial (encephalo) myopathies	Frequent (progressive, infantile onset and late onset; abnormalities of respiratory drive due to dysfunction of the respiratory centers are very frequently reported in pediatric cases)
Glycogen storage myopathies	Frequent in Pompe disease (infantile onset and late onset)

Occasional: < 10%; frequent: 10-50%; very frequent: > 50%; always present: 100%. DMD: Duchenne Muscular dystrophy; BMD: Becker Muscular dystrophy; DM1: Myotonic dystrophy type 1; LGMD: Limb girdle muscular dystrophy; FSHD: Facioscapulohumeral muscular dystrophy; CMD: Congenital muscular dystrophy; CM: Congenital myopathies; SMA: Spinal muscular atrophy; CMT: Charcot-Marie-Tooth disease

Table III. Swallowing difficulties in neuromuscular disorders.

Disorder	Swallowing difficulties
SMA type 1	Always present
SMA type 2	Very frequent
SMA type 3	Occasional
CMT	Occasional
DMD	Always present in the late stages of the disease
BMD	Occasional
DM1	Very frequent
LGMD	Occasional in some subtypes
FSHD	Occasional
CMD	Frequent in some subtypes
CM	Frequent in some subtypes
Mitochondrial (encephalo) myopathies	Frequent (more often due to central involvement than primary muscular impairment)
Glycogen storage myopathies	Frequent in Infantile onset Pompe Disease/rare in late onset Pompe Disease

Occasional: < 10%; frequent: 10-50%; very frequent: > 50%; always present: 100%. DMD: Duchenne Muscular dystrophy; BMD: Becker Muscular dystrophy; DM1: Myotonic dystrophy type 1; LGMD: Limb girdle muscular dystrophy; FSHD: Facioscapulohumeral muscular dystrophy; CMD: Congenital muscular dystrophy; CM: Congenital myopathies; SMA: Spinal muscular atrophy; CMT: Charcot-Marie-Tooth disease

ing [13,14,41]. The use of NIV associated with cough assist device (Mechanical Insufflation-Exsufflation, MI-E). and the early use of antibiotics are the standard of care in the event of airway infection both at home [28,29,42,46,47] and in hospitals [13,21,48-50]. In addition, oxygen should never be used unless associated with NIV and CO2 monitoring [13,28,29,36].

In case of hospitalization, chest x-ray should be performed as soon as possible to assess the presence of pneumonia or atelectasis. Furthermore, if there is no clear infectious cause, non-infectious causes of acute RF (pneumothorax, pulmonary thromboembolism, adipose embolism) should be excluded [13,36,51]. In patients with myopathy complicated by cardiomyopathy, an echocar-

Table IV. Cardiac complications in neuromuscular disorders.

	Cardiomyopathy	Arrhythmias	Conduction defects	Structural cardiac abnormalities
SMA type 1	Very rare (only one case reported)	Not reported	Not reported	Occasional
SMA type 2/3	Occasional	Occasional	Not reported	Occasional
CMT	Not reported	Not reported	Not reported	Not reported
DMD/ BMD	Very frequent (dilated cardiomyopathy)	Very frequent	Occasional	Occasional
DM1 (adult onset)	Occasional	Very frequent	Very frequent	Not reported
LGMD	Very frequent in some subtypes (LGMD1B and LGMD2C/D/E/I)	Occasional but very frequent in LGMD1B and frequent in LGMD2E	Occasional but very frequent in LGMD1B	Not reported
FSHD	Occasional	Occasional	Occasional	Not reported
CMD	Frequent in Fukuyama CMD; Occasional in other subtypes	Occasional	Occasional	Not reported
CM	Occasional	Occasional (Long QT)	Occasional	Not reported
Mitochondrial (encephalo) myopathies	Very frequent	Frequent	Frequent	Occasional
Glycogen storage myopathies	Very frequent in some subtypes (type II, III, IV, VII and IX)	Very frequent	Frequent	Not reported

Occasional: < 10%; frequent: 10-50%; very frequent: > 50%; always present: 100%. DMD: Duchenne Muscular dystrophy; BMD: Becker Muscular dystrophy; DM1: Myotonic dystrophy type 1; LGMD: Limb girdle muscular dystrophy; FSHD: Facioscapulohumeral muscular dystrophy; CMD: Congenital muscular dystrophy; CM: Congenital myopathies; SMA: Spinal muscular atrophy; CMT: Charcot-Marie-Tooth disease

Table V. Use of succinylcholine and inhaled anaesthetics in patients with NMDs.

	Use of succinylcholine	Use of halogenated agents
DMD/BMD	Must be avoided	Must be avoided
DM1	Must be avoided	Must be avoided
LGMD	Must be avoided	Must be avoided
FSHD	Must be avoided	Must be avoided
CMD	Must be avoided	Must be avoided
CM	Must be avoided	Must be avoided
Mitochondrial (encephalo) myopathies	Must be avoided	May be used
Glycogen Storage myopathies	Must be avoided	Must be avoided
SMA	Must be avoided	May be used
CMT	Must be avoided	May be used

DDMD: Duchenne Muscular dystrophy; BMD: Becker Muscular dystrophy; DM1: Myotonic dystrophy type 1; LGMD: Limb girdle muscular dystrophy; FSHD: Facioscapulohumeral muscular dystrophy; CMD: Congenital muscular dystrophy; CM: Congenital myopathies; SMA: Spinal muscular atrophy; CMT: Charcot-Marie-Tooth disease

diogram should also be performed in order to rule out the possibility of cardiogenic pulmonary oedema [13,36]. If the chest x-ray does not justify the clinical picture of acute RF, a chest CT scan must be required to exclude an anterior pneumothorax, not visible by the chest x-ray [13,36,51]. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism [13,36].

If non-invasive treatment (NIV and coughing assistance) fail, tracheal intubation must not be delayed [13,36,48]. In this case, difficulty in performing tracheal intubation

Table VI. Consensus summary of the 37 most relevant recommendations related to the urgent care of patients with NMDs

Section 1. ACUTE RESPIRATORY INSUFFICIENCY
1.1 Respiratory muscle weakness can impair the pump function of the respiratory system, upper airway muscle tone and secretion clearance efficiency. The respiratory consequences are retention of secretions, upper airway obstruction, nocturnal and finally daytime hypoventilation
1.2 Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections
1.3 If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax, adipose embolism or atelectasis). Cardiogenic pulmonary oedema should be ruled out in case of patients with myopathy
1.4 Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case, chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism
1.5 NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available
1.6 O2 must never be used except in association with NIV. If supplementary oxygen is required, titrate oxygen therapy to achieve a SpO2 94-98%, and monitor CO2
1.7 In the case of an acute, reversible event, intubation and invasive ventilation are indicated when NIV fails, unless prior directives are known to state otherwise. When indicated, tracheal intubation must not be delayed. It should be noted that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia, narrow and high-arch hard palate or limited mobility of the cervical spine
1.8 Upon recovery from acute illness, these patients should be promptly extubated by switching to NIV in combination with MI-E
1.9 Tracheotomy can be considered, in particular in patients with severe bulbar dysfunction. However, in acute phases it should only be considered in case of multiple weaning protocol failures including preventive application of NIV combined with MI-E after extubation
Section 2. CHOCKING DUE TO SWALLOWING DIFFICULTIES:
2.1 Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered
2.2 Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV
2.3 In case of choking, use MI-E or manual assisted coughing; if it is ineffective, consider emergent tracheal intubation
Section 3. CARDIAC COMPLICATIONS:
3.1 Cardiac dysfunction (i.e., cardiomyopathies or abnormalities of the conduction system and arrhythmias) may be present in these patients,in particular in patients with myopathies. However, the clinical manifestations of heart failure are often not recognized until very late, due to skeletal muscle limitations
3.2 As cardiomyopathy is progressive, consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias
3.3 Request patient's baseline test results, including echocardiogram and electrocardiogram
3.4 Obtain a brief history with particular attention to underlying cardiac status, including medication use
3.5 Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2
3.6 Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest x-ray and/or chest ultrasound may be useful if pulmonary oedema is suspected.
3.7 Obtain an echocardiogram and prompty consult a cardiologist.
3.8 As in patients with myopathies, the blood cardiac Tropo nin T (cTnT) levels may be chronically high, while the blood cardiac Troponin I (cTnI) level are more rarely elevated, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI

Table VI. continues

Section 4. ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT:
4.1 Ideally, surgery should occur in a specialist centre with staff experienced in managing these patients. Otherwise, urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management
4.2 Obtain a pre-operative evaluation that include lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. FVC less than 50% the predicted value, or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure, whenever possible
4.3 Patients and in particular patients with myopathies should also undergo careful assessment of heart function and optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram are mandatory before anaesthesia
4.4 In many patients with NMDs the use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis (see table 5)
4.5 Patients with NMDs may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex)
4.6 Tracheal intubation may be difficult in patients with NMDs and a frequent use of fiberoptic-assisted endotracheal intubation is reported
4.7 The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia side-effects and reduction of postoperative respiratory complications
4.8 Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea.
4.9 Admission to an Intensive Care Unit (ICU) should be considered in patient at risk for respiratory or cardiac complications
4.10 Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation and switching to NIV with aggressive use of MI-E. O2 must never be used, except in association with NIV
Section 5. FALLS AND FRACTURES:
5.1. Due to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures
5.2 In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows for early walking recovery while preserving muscle function
5.3 In non-ambulatory adult patients, conservative management may be considered for non-displaced sub capital femoral neck fractures. Conversely, internal fixation is required in diaphyseal or trochanteric femoral fractures.
5.4 The treatment of femoral fractures in paediatric patients is strictly related to the child's age, site of the fracture, and disability related to muscle weakness. Conservative treatment may be considered in patients younger 5-6 years, with non-displaced fractures, and when a short period of immobilization is expected. In other cases, surgical fixation using minimally invasive techniques (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators) is preferred
Section 6. ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION:
6.1 Patients with NMDs and especially older patients can experience constipation due to abnormal gastrointestinal motility
6.2 Gastric and/or abdominal distention can cause acute respiratory failure in patients at high risk of respiratory complications. In these cases, gastrointestinal decompression by nasogastric tube and/or rectal tube is often an effective therapy
Section 7. OTHER ISSUES
7.1 Blood transaminases and creatine kinase levels may be increased in patients with myopathies. If other hepatic function tests (e.g., bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy liver disease and may be due to muscle involvement

is frequently reported [30,52,53]. This may be due to several factors such as jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia, narrow and high-arch hard palate or limited mobility of the cervical spine [52,53].

In addition, it is important to verify whether an invasive cure plan has been shared before with the referral medical team and the patient had previously approved invasive manoeuvres such as tracheostomy, also in the context of expressed end-of-life decisions depending of

time of progression of the NMDs. A consultation with the referring team may be sometimes essential. If there are not informations regarding a previously approved invasive cure plan by the patient, it is important to verify if the patient is able to do it during the acute setting.

This should be done prior to proceeding with invasive manoeuvres. If the patient is unable to express end-of-life decisions due to age, severe clinical conditions or inability to communicate for other reasons (e.g., anarthria, cognitive impairment), it is good clinical practice to discuss about the patient choices with caregivers or close family members.

In the acute phase, tracheostomy should be considered only after failure of multiple attempts at proper weaning, that includes preventive application of NIV combined with MI-E immediately after extubation [31,32].

Based on these considerations, the section on respiratory involvement in the EC includes the following statements.

1.1 Respiratory muscle weakness can impair the pump function of the respiratory system, upper airway muscle tone and secretion clearance efficiency. The respiratory consequences are retention of secretions, upper airway obstruction, nocturnal and finally daytime hypoventilation.

1.2 Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute RF and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections.

1.3 If no infectious cause of acute RF is evident, consider non-infectious causes (e.g., pneumothorax, adipose embolism or atelectasis). Cardiogenic pulmonary oedema should be ruled out in case of patients with myopathy.

1.4 Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 < 95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case, chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism.

1.5 NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an AMBU bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available.

1.6 O2 must never be used except in association with NIV. If supplementary oxygen is required, titrate oxygen therapy to achieve a SpO2 94-98%, and monitor CO2.

1.7 In the case of an acute, reversible event, intubation and invasive ventilation are indicated when NIV fails, unless prior directives are known to state otherwise. When indicated, tracheal intubation must not be delayed. It should be noted that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia, narrow and high-arch hard palate or limited mobility of the cervical spine.

1.8 Upon recovery from acute illness, these patients should be promptly extubated by switching to NIV in combination with MI-E.

1.9 Tracheotomy can be considered, in particular in patients with severe bulbar dysfunction. However, in acute phase it should only be considered in case of multiple weaning protocol failures including preventive application of NIV combined with MI-E after extubation.

Chocking due to swallowing difficulties

Inadequate strength and coordination of the bulbar muscles, is common in patients with NMDs and leads to difficulty in swallowing (dysphagia) and managing saliva (sialorrhea) [54,55]. A meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, malnutrition, sialorrhea and choking when eating or drinking are signs and symptoms potentially associated with swallowing difficulties [54,56]. The swallowing impairments vary with the natural course of the underlying NMD (Tab. III). Bulbar dysfunction may cause chocking, aspiration pneumonia and other pulmonary sequelae, such as pulmonary fibrosis [54,57-59]. In addition, it impairs the ability to clear airway secretions [14]. The association of a weak cough with dysphagia increases the risk for choking and aspiration pneumonia [60]. On the other hand, bulbar dysfunction may impede the successful use of NIV [32,48].

In case of choking, the use of MI-E may reverse hypoxemia [61]; if hypoxemia cannot be corrected by MI-E, emergent tracheal intubation should be immediately considered [13].

Based on these considerations, the section on swallowing difficulties in the EC includes the following statements.

2.1 Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered.

2.2 Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV.

2.3 In case of choking, use MI-E or manual assisted coughing; if it is ineffective, consider emergent tracheal intubation.

Cardiac complications

Cardiac involvement is frequently reported in patients affected by NMDs with a growing impact on mor-

bidity and mortality [62-66]. Two major features are usually described: i) cardiomyopathy; and ii) conduction defects with arrhythmias [63,66-69]. The incidence and nature of cardiac involvement vary according to the type of NMD (Tab. IV).

Cardiac evaluation includes physical examination, electrocardiogram, transthoracic echocardiogram, Holter monitoring, cardiac MRI and laboratory analysis including B-type natriuretic peptide [63,73-76]. A scheduled follow up is usually preferred because most of these patients are asymptomatic due to musculoskeletal limitations [63,73,78,79]. Symptoms of cardiac insufficiency in wheel-chair-bound patients may present with loss of appetite, weight reduction, gastrointestinal disorders (slow digestion, stomach pain, pain in the upper right side of the abdomen), palpitations, dyspnoea at rest, orthopnoea, pre-syncope, syncope [80].

Appropriate cardiac treatment significantly improves the overall long-term outcome of NMDs [67]. Standard heart failure treatment, such as ACE inhibitors and/or beta-blockers, is currently used in patients presenting with dilated cardiomyopathy [70,80,81]. However, beta-blockers should be avoided in patients with conduction system disorders [73,82]. New drugs for heart failure improving survival in NMDs are now available [83-86].

Electrical therapy can also be useful in NMD patients: the implant of pacemakers (PMs) is indicated in case of bradycardia or atrioventricular blocks, whereas ventricular arrhythmias and/or severe congestive heart failure may require automatic implantable cardioverter defibrillator (ICD) placement [73,87]. Heart transplantation is an effective treatment for a selected group of patients with NMDs and end-stage heart failure (e.g., Becker MD or Steinert disease) [88-91]. Left ventricular–assist devices can be used for long term treatment in patients with Duchenne MD and severe cardiomyopathy [80].

Patients with heart failure may also benefit of the use of nocturnal NIV for respiratory support. Indeed, NIV results in improved gas exchange and heart pump function [73].

The following statements are suggested for patients with NMDs at risk of cardiac complications.

3.1 Cardiac dysfunction (i.e., cardiomyopathies or abnormalities of the conduction system and arrhythmias) may be present in these patients, in particular in patients with myopathies. However, the clinical manifestations of heart failure are often not recognized until very late, due to skeletal muscle limitations.

3.2 As cardiomyopathy is progressive, consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias.

3.3 Request patient's baseline test results, including echocardiogram and electrocardiogram.

3.4 Obtain a brief history with particular attention to underlying cardiac status, including medication use.

3.5 Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2.

3.6 Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest x-ray and/or chest ultrasound may be useful if pulmonary oedema is suspected.

3.7 Obtain an echocardiogram and promptly consult a cardiologist.

3.8 As in patients with myopathies, the blood cardiac Troponin T (cTnT) levels may be chronically high, while the blood cardiac Troponin I (cTnI) level are more rarely elevated, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.

Anaesthetic and perioperative management

Patients with NMDs may have abnormal vital functions (e.g., respiratory and/or cardiac involvement), which increase the risk of surgical procedures requiring general anaesthesia [92,93]. In addition, some anaesthetic agents can trigger life-threatening reactions (i.e., malignant hyperthermia, rhabdomyolysis and hyperkaliaemic cardiac arrest secondary to denervation) [94-96]. As a consequence, patients with NMDs are at high risk of intra-operative and post-operative complications, and surgery should be, ideally, performed in a fully equipped hospital with extensive experience in NMDs management [93].

Pre-operative assessment of respiratory function should include lung function tests and cough assessment [92,93]. Patients with respiratory muscle weakness [i.e. forced vital capacity (FVC) less than 50% of predicted value, or peak cough less than 270 l/min], should be trained pre-operatively on the use of NIV and mucus clearance techniques [92,93]. Indeed, when general anaesthesia is necessary, these patients should be extubated by switching directly to NIV in combination with MI-E [30,92,93, 97,98].

Patients with myopathies should also undergo a careful assessment of heart function and optimize cardiac therapy in the pre-operative period [93,94,98].

Patients with NMDs may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants [94]. Moreover, the use of inhaled anaesthetics and succinylcholine is contraindicated in myopathic patients due to the high risk of acute rhabdomyolysis [93-96,99-100] (Tab. V). In addition, difficulty in performing direct laryngoscopy and the frequent use of fibreoptic-assisted endotracheal intubation is frequently reported [30,52,53]. As a consequence, regional anaesthesia should be warranted whenever possible [30,93,94,98].

Based on these considerations, the following statements are suggested, in the section on anaesthetic and perioperative management.

4.1 Ideally, surgery should occur in a specialist centre with staff experienced in managing these patients. Otherwise, urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

4.2 Obtain a pre-operative evaluation that include lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. FVC less than 50% the predicted value, or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure, whenever possible.

4.3 Patients with NMDs, in particular patients with myopathies, should also undergo careful assessment of heart function and optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram are mandatory before anaesthesia.

4.4 In many patients with NMDs the use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis (see table V).

4.5 Patients with NMDs may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex).

4.6 Tracheal intubation may be difficult in patients with NMDs and a frequent use of fiberoptic-assisted endotracheal intubation is reported.

4.7 The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia side-effects and reduction of postoperative respiratory complications.

4.8 Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea.

4.9 Admission to an Intensive Care Unit (ICU) should be considered in any patient who is at risk for respiratory or cardiac complications.

4.10 Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation and switching to NIV with aggressive use of MI-E. O2 must never be used, except in association with NIV.

Falls and fractures

Fractures are quite common in patients with NMDs, as they present marked disuse osteoporosis and are at high risk of falls [101]. Decreased bone mass and osteopenia are reported in approximately 2/3 of these patients, resulting in frequent fragility fractures [102]. Goals of the treatment are to promptly restore function and to reduce immobilization in order to prevent bed rest consequences, such as muscular and bone weakness that may increase the risk of re-fractures [103].

In adult patients, non-surgical treatment with cast immobilization is generally recommended for non-ambulatory patients, except for patients with inter-trochanteric, sub-trochanteric, and diaphyseal fractures. On the other hand, a prolonged immobilization (> 4 weeks) that aggravates muscle wasting and disuse osteoporosis, should be avoided in ambulatory patients. As a consequence, all ambulatory and non ambulatory patients, who present inter-trochanteric, sub-trochanteric, and diaphyseal fractures, generally benefit from surgical stabilization. Intramedullary nails or plates are used to allow early extremity range of motion and to promote acceleration of the fracture healing [1]. However, the level of independence and disability before the fall and fracture is usually unlike to be maintained after surgery, regardless of the level of surgery because of the underlying muscle weakness.

In paediatric patients, conservative treatment may be considered in children younger than 5-6 years, with non-displaced fractures and when a short period of immobilization is expected. In other cases, surgical fixation using minimally invasive techniques (e.g., flexible intramedullary nailing) is preferred [104].

Based on these considerations, the section on falls and fractures in EC includes the following statements.

5.1 Due to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures.

5.2 In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows for early walking recovery while preserving muscle function.

5.3 In non-ambulatory adult patients, conservative management may be considered for non-displaced sub capital femoral neck fractures. Conversely, internal fixation is required in diaphyseal or trochanteric femoral fractures.

5.4 The treatment of femoral fractures in paediatric patients is strictly related to the child's age, site of the fracture, and disability related to muscle weakness. Conservative treatment may be considered in patients younger than 5-6 years, with non-displaced fractures, and when a short period of immobilization is expected. In other cases, surgical fixation using minimally invasive techniques (e.g., percutaneous fixation by Kirshner wires and plaster casts, flexible intramedullary nailing or light external fixators) is preferred.

Acute constipation due to bowel dysfunction

Constipation characterized by abdominal pain and distension, associated with the inability to defecate, is

extremely common in patients with NMDs [1,105]. Multiple potential risk factors can contribute to the development of constipation in NMDs, including underlying motility dysfunction due to involvement of smooth muscle fibres, lack of mobility, dehydration due to swallowing dysfunction, and lack of dietary fibre. Gastric or abdominal distention can cause acute RF in patients with severe respiratory muscle weakness. Treatment strategies include increasing water and fibre intake, and using osmotic laxatives. Decompressive manoeuvres (i.e., placing nasogastric and/or rectal tubes) are the mainstay of acute management [105].

Based on these considerations, the following statements are suggested in the section on acute constipation due to bowel dysfunction.

6.1 Patients with NMDs and especially older patients can experience constipation due to abnormal gastrointestinal motility.

6.2 Gastric and/or abdominal distension can cause acute respiratory failure in patients at high risk of respiratory complications. In these cases, gastrointestinal decompression by nasogastric tube and/or rectal tube is often an effective therapy.

Other issues

Muscle can also be a source of elevation in serum aminotransferases. As a consequence, abnormal liver function tests are frequently observed in cases of myopathies. Serum aminotransferases lack tissue specificity to allow clinicians to distinguish primary liver injury from muscle damage [106,107]. This can raise the question of liver injury and often triggers a false pathway of investigation.

Based on these considerations, the following statement is included in EC.

7.1 Blood transaminases and creatine kinase levels may be increased in patients with myopathies. If other hepatic function tests (e.g., bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy liver disease and may be due to muscle involvement.

Discussion

This paper reports the results of the first Consensus Conference organized to build specific ECs for NMDs. Aim of the workshop was to agree on a minimum set of the most relevant management information and recommendations related to urgent care, and to produce ECs dedicated to patients with NMDs.

Consensus was reached on key issues and management of the main clinical problems requiring urgent care (i.e., acute RF, chocking, cardiac complications, anaesthesia, fractures and acute constipation) and are summarized in 4 tables and 37 statements. Based on these statements the CWG defined 13 ECs, one for each NMD, all sharing the same structure but with disease-related specificities.

Although NMDs may lead to severe disability and may shorten the life-expectancy, improvements in the function, quality of life and longevity of these patients have been achieved through a multidisciplinary management approach [2,4,8,10,11,12,14,18]. Consequently, when these patients come to the Emergency Department due to acute life-threatening complications, they deserve full appropriate care and treatment. In order to optimise patient outcomes, the medical providers should have a good background in the issues relevant for individuals with NMDs. However, these diseases are rare and are an uncommon cause of admission to Emergency Departments [33]. For this reason, the local ED physicians might be inexperienced in the management of these patients [5,34]. The ECs proposed in this paper may provide not only a rapid overview of key issues related to the more frequent acute complications in patients with NMDs, but also describe the background information which is required to better improve local urgent care.

We are aware that this study has several limitations. One may argue that the level of information is high for an acute setting, but we believe that providing the background of the disease issues for the specific domain or organ involved will help the physicians in the emergency setting. A second limitation may be that we considered different forms of NMDs, which may differ in terms of disease onset, progression and severity. However, many studies have shown that several NMDs share common features and issues concerning respiratory and cardiac impairment, swallowing difficulties and perioperative management, while retaining disease-specific problems [13,14,62,86]. Another limitation may be that many statements selected by the Consensus panel were mainly derived from observational studies and expert's opinion rather than evidence-based guidelines. However, prospective randomized controlled trials aimed at supporting the utility of some therapies such as NIV and MI-E, would be difficult to carry out for ethical reasons. Indeed, in developed Countries of the world NIV and MI-E are routinely used to treat patients with NMDs and acute respiratory complications.

In conclusion, this paper reports a minimum set of management recommendations for urgent care dedicated to patients with NMDs, suggested by a panel of Italian experts. Based on these statements, we propose an EC for each selected NMD. The usefulness of these ECs in improving local acute care will be verified in the acute setting and real-world evidence.

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Conflict of interest statement

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Not applicable.

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ON-LINE SUPPORTING INFORMATION

Table S1: Emergency card for patients with Spinal muscular atrophy (SMA) type 1

EMERGENCY CARD for patients with **Spinal muscular atrophy (SMA) type 1**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are always present (early onset; frequent exacerbation). Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and daytime hypoventilation.. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are always present. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Cardiomyopathy is very rare (only one 1 case reported). Conduction defects and arrhythmia are not reported. Structural cardiac abnormalities are occasional.
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Use of succinylcholine must be avoided to prevent succinylcholine-induced hyperkalaemia. Inhaled anaesthetics may be used. ✓ They may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex).

	✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Osteoporosis increases the risk of fractures ✓ In adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ Gastroesophageal reflux can occur in SMA. Symptoms may be subtle (weight loss, poor feeding, crying after feed or when lying down and coughing). If a gastrostomy is performed, and reflux is present, a Nissen fundoplication should be associated

Table S2: Emergency card for patients with Spinal muscular atrophy (SMA) type 2

EMERGENCY CARD for patients with **Spinal muscular atrophy (SMA) type 2**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are very frequent. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Cardiomyopathies, arrhythmias and structural cardiac abnormalities are occasional. Conduction defects are not reported.
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Use of succinylcholine must be avoided to prevent succinylcholine-induced hyperkalaemia. Inhaled anaesthetics may be used. ✓ They may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported.

	✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility. ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ Gastroesophageal reflux can occur in SMA. Symptoms may be subtle (weight loss, poor feeding, crying after feed or when lying down and coughing). If a gastrostomy is performed, and reflux is present, a Nissen fundoplication should be associated.

Table S3: Emergency card for patients with Spinal muscular atrophy (SMA) type 3

EMERGENCY CARD for patients with **Spinal muscular atrophy (SMA) type 3**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are occasional. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation.. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are occasional. ✓ Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Cardiomyopathies, arrhythmias and structural cardiac abnormalities are occasional. Conduction defects are not reported.
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Use of succinylcholine must be avoided to prevent succinylcholine-induced hyperkalaemia. Inhaled anaesthetics may be used. ✓ They may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex).

	✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ Gastroesophageal reflux can occur in SMA. Symptoms may be subtle (weight loss, poor feeding, crying after feed or when lying down and coughing). If a gastrostomy is performed, and reflux is present, a Nissen fundoplication should be associated

Table S4: Emergency card for patients with Charcot-Marie-Tooth disease (CMT)

EMERGENCY CARD for patients with **Charcot-Marie-Tooth disease (CMT)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are occasional in some subtypes. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation.. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are occasional. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Not reported
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Use of succinylcholine must be avoided to prevent succinylcholine-induced hyperkalaemia. Inhaled anaesthetics may be used. ✓ They may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported.

	✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ Pain is a very common. It can be caused by altered loading of the joints, because of muscle weakness, or neuropathic pain, owing to damage to the pain nerve endings.

Table S5: Emergency card for patients with Duchenne Muscular Dystrophy

EMERGENCY CARD for patients with **DUCHENNE MUSCULAR DYSTROPHY (DMD)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are always present in adulthood. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). In case of long-bone or vertebral fractures consider fat embolism syndrome if patient has dyspnoea or altered mental status. Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are always present in the late stage of the disease. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy and arrhythmia are very frequent. Conduction defects are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ In case of chronic corticosteroid therapy consider adrenal insufficiency. Determine whether stress steroid dosing is necessary. For critical adrenal insufficiency, administer 100 mg hydrocortisone by slow intravenous injection or intramuscular. In less critical situations, consult the PJ Nicholoff Steroid and obtain early consultation with an endocrinologist.

Table S6: Emergency card for patients with Becker Muscular dystrophy (BMD)

EMERGENCY CARD for patients with **Becker Muscular dystrophy (BMD),**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are occasional. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). In case of long-bone or vertebral fractures consider fat embolism syndrome if patient has dyspnoea or altered mental status. Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are occasional. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy and arrhythmia are very frequent. Conduction defects are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ In case of chronic corticosteroid therapy consider adrenal insufficiency. Determine whether stress steroid dosing is necessary. For critical adrenal insufficiency, administer 100 mg hydrocortisone by slow intravenous injection or intramuscular. In less critical situations, consult the PJ Nicholoff Steroid and obtain early consultation with an endocrinologist.

Table S7: Emergency card for patients with Myotonic dystrophy type 1 (DM1)

EMERGENCY CARD for patients with **Myotonic dystrophy type 1 (DM1)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. Central sleep apnoea are also reported. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are very frequent. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Conduction defects and arrhythmia are very frequent. Dilated cardiomyopathy is occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV. ✓ In these patients respiratory insufficiency may be caused both by weakness or myotonic reactions, which may involve laryngeal and respiratory. Many factors like hypothermia, postoperative shivering, dyskalemia, mechanical and electrical stimulation or drugs (i.e., propranolol, succinylcholine and anticholinesterase agents) can precipitate myotonic contractures. Myotonia occurs for an intrinsic change in the muscle and not in the peripheral nerve or neuromuscular junction. Thus, it cannot be abolished by peripheral nerve blockades or neuromuscular blockers. Myotonia may be treated with midazolam, otherwise the treatment is mainly preventive, avoiding all triggering factors.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases, gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ Intellectual impairment and cognitive dysfunction are often present. ✓ Excessive daytime sleepiness (EDS) is common and is most often owing to CNS involvement. Sleep apnoea and chronic respiratory failure also need to be considered and sleep study should be considered to assess possible obstructive sleep apnoea and CNS mediated sleep apnoea. ✓ DM1 may be associated with insulin resistance and cataract.

Table S8: Emergency card for patients with Facio-scapulo-humeral muscular dystrophy (FSHD)

EMERGENCY CARD for patients with **Facio-scapulo-humeral muscular dystrophy (FSHD)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are occasional. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are occasional. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy, conduction defects and arrhythmia are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible.

	✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ Conjunctivitis and ulceration of the cornea can occur owing to limited blinking and inability to properly close the eyes, also when sleeping.. ✓ Substantial facial muscle weakness may lead to misinterpretation of emotional expression, particularly in those with severe, childhood-onset FSHD.

Table S9: Emergency card for patients with Limb girdle muscular dystrophy (LGMD)

EMERGENCY CARD for patients with **Limb girdle muscular dystrophy (LGMD)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent in some subtypes (LGMD1, LGMD2C/D/E/F). Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation.. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are occasional in some subtypes. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy is very frequent in some subtypes (LGMD1B and LGMD2C/D/E/I). Conduction defects and arrhythmia are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ Some subtypes of LGMD can have central nervous system involvement with intellectual disability and/or epilepsy and, rarely, movement disorders.

Table S10: Emergency card for patients with Congenital muscular dystrophy (CMD)

EMERGENCY CARD for patients with **Congenital muscular dystrophy (CMD)**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent in some subtypes (Ullrich's CMD, LAMA 2 deficient CMD). Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are frequent in some subtypes. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy is frequent in Fukuyama CMD and occasional in other subtypes. Conduction defects and arrhythmia are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement.

Table S11: Emergency card for patients with Congenital Myopathies

EMERGENCY CARD for patients with **Congenital Myopathies**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent in some subtypes (Nemaline, Myofibrillary and Centro-nuclear CM). Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that in these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are frequent in some subtypes. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy, conduction defects and arrhythmia (Long QT) are occasional. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis and malignant hyperthermia. ✓ Malignant hyperthermia is a medical emergency characterized by pathological hyperthermia, muscle rigidity, and hypermetabolism in response to triggering anaesthetic agents (i.e., succinylcholine and inhaled anaesthetics), It must be treated with dantrolene and additional supportive care measures. ✓ They may experience increased sensitivity to sedatives, anaesthetics agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement.

Table S12: Emergency card for patients with Mitocondrial myopathies

EMERGENCY CARD for patients with **Mitocondrial myopathies**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent (Progressive, infantile onset and late onset). Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation. Abnormality of respiratory drive due to dysfunction of the respiratory centers are very frequently reported in pediatric cases ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that n these patients tracheal intubation may be difficult. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are frequent (more often due to central involvement than primary muscular impairment). Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy is very frequent Conduction defects and arrhythmia are frequent. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist.
ANAESTHETIC PRECAUTIONS AND PERIOPERATIVE MANAGEMENT	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management. ✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia.

	✓ As these patients may have increased lactate levels during periods of physiological stress, preoperative fasting could be particularly hazardous. Thus, i.v. isotonic fluid containing dextrose (e.g., 0.9% sodium chloride with 5% dextrose) should be started during preoperative fasting period to allow maintenance of normoglycemia to avoid excessive glycolytic oxidation that may increase plasma lactate levels. ✓ Use of succinylcholine must be avoided to prevent rhabdomyolysis. Inhaled anaesthetics can be administered in order to avoid prolonged use of propofol, which can increases lactic acidosis. ✓ They may experience increased sensitivity to sedatives, inhaled anaesthetics and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general a and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 should not be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures. ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required. ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ A major clue to mitochondrial disease is a multisystem involvement, that may include: o Brain – stroke-like episodes, seizures, myoclonus, ataxia, developmental delay or regression, dementia, migraine, and dystonia o Eye – pigmentary retinopathy, optic atrophy, and cataracts o Neuropathy and dysautonomia o Endocrine – diabetes and hypoparathyroidism o Kidney – proximal nephron dysfunction and glomerulopathy o Gastrointestinal – altered motility, liver disease, episodes of nausea and vomiting, and exocrine pancreatic dysfunction o Hematologic – sideroblastic anaemia and pancytopenia o Metabolic acidosis due to elevated levels of lactate ✓ Lactate levels may be elevated, normal or only minimally elevated. These patients may have elevated lactate levels only during periods of physiologic stress. It is controversial whether IV sodium bicarbonate should be used. Many authors recommended that it should be reserved for cases of extreme acidosis when the blood pH is <7.2. ✓ Intellectual impairment and cognitive dysfunction may be present. ✓ Mitochondrial myopathies may worsen during periods of increased physiologic stress, such as an illness or surgery/anaesthesia. During these periods rhabdomyolysis may occur. ✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement.

Table S13: Emergency card for patients with Metabolic (Glycogen storage) myopathies

EMERGENCY CARD for patients with **Metabolic (Glycogen storage) myopathies**	
Name _____ Date of birth _____ Fiscal Code _____ If presenting at an emergency department, contact the neuromuscular and/or respiratory team at: _____as soon as possible on: _____	
MAIN TOPICS	***MOST RELEVANT INFORMATIONS AND RECOMMENDATIONS RELATED TO THE EMERGENCY CARE***
ACUTE RESPIRATORY INSUFFICIENCY	✓ Respiratory complications are frequent in Glycogen storage disease type II (Pompe Disease) both in infantile and late onset form. Respiratory muscles weakness can compromise pump function of the respiratory system, upper airway muscles tone and efficiency of secretion clearance. The respiratory consequences are secretion retention, upper airway obstruction, nocturnal and finally daytime hypoventilation.. ✓ Respiratory infections (i.e., tracheobronchitis or pneumonia) are the most frequent cause of acute respiratory failure and require early management. Low threshold for empiric antibiotic therapy is recommended for chest infections. ✓ If no infectious cause of acute respiratory failure is evident, consider non-infectious causes (e.g., pneumothorax or atelectasis). Cardiogenic pulmonary oedema should be also ruled out. ✓ Collect respiratory symptoms and monitor SpO2 levels via pulse oximetry; even mild hypoxaemia (e.g., SpO2 <95% in room air) is a concern and requires a chest x-ray and a blood gas analysis test. Chest x-ray may be difficult to interpret, especially in the presence of scoliosis. In this case chest CT scan may be useful in order to rule out pneumothorax, pneumonia or atelectasis. If even chest CT scan does not show any cause for acute RF, it is useful to deepen the examination by administering contrast medium to exclude a pulmonary thromboembolism. ✓ NIV is often required. In addition, assisted coughing (i.e., breath-stacking techniques with an Ambu bag combined with compression of the chest wall or abdomen) or cough assist device (MI-E) help to clear airways secretions. Use the patient's home equipment when available. ✓ O2 must never be used without associating it with NIV. If supplemental oxygen is required titrate oxygen therapy to achieve SpO2 94-98% and monitor CO2. ✓ In case of an acute, reversible event intubation and invasive ventilation is indicated when NIV failure occurs (unless there is a known advance directive stating otherwise). When indicated tracheal intubation must not be delayed. Consider that n these patients tracheal intubation may be difficult due to jaw ankylosis, atrophy of the masseter muscle and/or other masticatory muscles, macroglossia or limited mobility of the cervical spine. ✓ After recovery from the acute illness, these patients should be promptly extubated to NIV combined with MI-E. Tracheotomy can be evaluated in particular in patients with severe bulbar dysfunction. However, in the acute phase it should be considered only in the case of multiple failures of weaning protocol including preventive application of NIV combined with MI-E after extubation.
CHOCKING DUE TO SWALLOWING DIFFICULTIES	✓ Swallowing difficulties are frequent in Infantile onset Pompe Disease, rare in late onset Pompe Disease. Signs and symptoms of swallowing difficulties such as a meal time longer than 30 minutes, recurrent chest infections, unintentional weight loss, and choking when eating or drinking should be considered. ✓ Severe bulbar dysfunction increases the patient risk for aspiration and hampers the elimination of airway secretions. In addition, it may impede successful use of NIV. ✓ In case of choking use MI-E or manual assisted coughing; if it is ineffective consider emergent tracheal intubation
ACUTE CARDIAC COMPLICATIONS	✓ Dilated cardiomyopathy is very frequent in some subtypes (type II, III, IV, VII and IX). In the infantile form of Pompe disease hypertrophic cardiomyopathy may be present. Conduction defects and arrhythmia are frequent. However, clinical manifestations of heart failure are often unrecognized until very late, owing to musculoskeletal limitations. ✓ Consider worsening cardiomyopathy and rule out congestive heart failure, atrio-ventricular blocks and arrhythmias. ✓ Ask for the patient's baseline test results, including echocardiogram and electrocardiogram. ✓ Obtain a brief history with a focus on baseline cardiac status, including use of medications. ✓ Ask about cardiac symptoms and monitor heart rate rhythm, blood pressure and SpO2. ✓ Measure blood levels of B-type natriuretic peptide and obtain an electrocardiogram; a chest radiograph and/or chest ultrasound may be useful if pulmonary oedema is suspected. ✓ Obtain an echocardiogram and early consultation with a cardiologist. ✓ In these patients blood level of cardiac Troponin T (cTnT) may be chronically high, while blood level of cardiac Troponin I (cTnI) are more rarely high. Consequently, in the case of suspected myocarditis or myocardial ischemia, it is recommended to measure cTnI.
ANAESTHETIC PRECAUTIONS AND	✓ Ideally, surgery should occur in a specialist centre with staff experienced in managing these individuals. Otherwise, the urgent surgical interventions may be performed in non-specialized centres following recommendations regarding anaesthesia and perioperative management.

PERIOPERATIVE MANAGEMENT	✓ Obtain a pre-operative evaluation including lung function tests and cough assessment; if respiratory muscle weakness is present (i.e. forced vital capacity less than 50% of predicted value or peak cough less than 270 l/min), familiarization with ventilatory support (i.e., MI-E and NIV) should be warranted prior to procedure whenever possible. ✓ Patients should also undergo careful assessment of heart function as well as optimization of cardiac therapies in the pre-operative period. An electrocardiogram and echocardiogram should be performed before anaesthesia. ✓ Use of succinylcholine and inhaled anaesthetics must be avoided to prevent rhabdomyolysis ✓ They may experience increased sensitivity to sedatives, anaesthetic agents and muscle relaxants; thus, the depth of anaesthesia and the neuromuscular function should be monitored in order to titrate the appropriate dose of those drugs. In addition, the effect of muscle relaxants should be completely reversed at the end of surgery (i.e., rocuronium should be used and must be reversed by sugammadex). ✓ In the infantile form of Pompe disease with significant hypertrophic cardiomyopathy, decreased cardiac output and myocardial ischemia have been observed during anaesthesia. In fact, stiffness of the hypertrophied ventricular walls can induce abnormal diastolic relaxation and lead to dynamic left ventricular outflow tract obstruction, elevated left ventricular end-diastolic pressure and reduced diastolic filling. Such a condition may precipitate as a consequence of a decrease in systemic vascular resistance, preload, or both eventually induced by anaesthetic agents, with an increased risk of intraoperative cardiac arrest. ✓ Tracheal intubation may be difficult in patients with NMDs and frequent use of fibreoptic-assisted endotracheal intubation is reported. ✓ The use of regional or local anaesthesia offers a significant advantage in term of avoidance of general anaesthesia and reduction of postoperative respiratory complications. ✓ Morphine infusions should be avoided, mainly in patients with reduced respiratory function or obstructive sleep apnoea ✓ Admission to an Intensive Care Unit should be considered in any patient who is at risk for respiratory or cardiac complications. Patients with decreased respiratory muscle strength require close monitoring and aggressive post-operative respiratory management including early extubation to NIV with aggressive use of MI-E. O2 must never be used without associating it with NIV.
FALLS AND FRACTURES	✓ Owing to weakness, contractures and poor balance, patients with NMDs are at high risk of frequent falls. On the other hand, osteoporosis increases the risk of fractures ✓ In ambulatory adult patients, internal fixation of femoral fracture is preferable to conservative treatment because it allows early walking recovery, preserving muscle function. ✓ In non-ambulatory adult patients, conservative treatment can be considered in case of non-displaced sub capital femoral neck fracture. On the contrary, in diaphyseal or trochanteric femoral fracture internal fixation is required ✓ In paediatric patients the treatment of femoral fractures is strictly related with the age of the child, the site of the fracture and the disability related to muscle weakness. Conservative treatment can be considered in patients under 5-6 years of age, with non-displaced fractures and when a short period of immobilization is expected. In the other cases surgical fixation using minimally invasive techniques is preferred (e.g., percutaneous fixation by Kirshner wires and plaster casts, Flexible Intramedullary Nailing or light external fixators).
ACUTE CONSTIPATION DUE TO BOWEL DYSFUNCTION	✓ Some patients can experience constipation due to abnormal gastrointestinal motility ✓ Gastric and/or abdominal distention may cause acute respiratory failure in patients at high risk of respiratory complications. In these cases gastrointestinal decompression by using of a nasogastric tube and/or rectal tubes is often an effective therapy.
OTHER ISSUES	✓ In these patients blood levels of transaminases and creatine kinase may be increased. If other hepatic function tests (e.g. bilirubin and gamma GT) are normal, this pattern doesn't necessarily reflect hepatopathy and may be due to muscle involvement. ✓ Metabolic myopathy presenting with exercise intolerance (e.g. McArdle's disease) may present with acute rhabdomyolysis with severe hyperCKemia, muscle pain, and myoglobinuria. During such events, there is a risk of acute renal failure.

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Is paravertebral muscles edema a consequence of neurogenic changes in MuSK-positive myasthenia gravis?

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Anti-MuSK myasthenia gravis (Anti-MuSK MG) is a chronic autoimmune disease caused by complement-independent dysfunction of the agrin-MuSK-Lrp4 complex, accompanied by the development of the pathological muscle fatigue and sometimes muscle atrophy. Fatty replacement of the tongue, mimic, masticatory and paravertebral muscles, revealed by muscle MRI and proton magnetic resonance spectroscopy (MRS), is considered to be a consequence of the myogenic process in anti-MuSK antibody MG in the patients with a plenty long course of the disease. However, in most experimental studies on animal models with anti-MuSK MG, complex presynaptic and postsynaptic changes are revealed, accompanied by the functional denervation of masticatory and paravertebral muscles predominantly. This study presents the MRI, nerve conduction studies (NCS), repetitive nerve stimulation (RNS) and electromyography (EMG) of neurogenic lesions of the axial muscles (m. Multifidus Th12, L3-L5; m. Erector spinae L4-L5) in two patients K. (51 years old), and P. (44 years old), both of whom were having weakness of the paravertebral muscles for 2-4 months due to anti-MuSK MG. The clinical manifestations, as well as the edematous changes in the paravertebral muscles, regressed after therapy. Thus, these clinical examples may confirm the presence of the neurogenic changes at an early stage of anti-MuSK myasthenia gravis and indicate importance of immediate initiation of therapy to avoid the development of muscle atrophy and fatty infiltration.

Key words: antibodies to MuSK, muscle MRI, neurogenic muscle edema, anti-MuSK myasthenia gravis

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Introduction

Anti-MuSK antibody myasthenia gravis (Anti-MuSK MG) is a chronic autoimmune disease caused by complement-independent dysfunction of the agrin-MuSK-Lrp4 complex, accompanied by the development of pathological muscle fatigue and sometimes muscle atrophy. Anti-MuSK MG is a subtype of seronegative acquired myasthenia gravis, occurring in 5-8% of all cases [1-3].

Four main clinical phenotypes of anti-MuSK MG were described: generalized form, oculobulbar form, lumbar-limb phenotype with involvement of the neck extensors and respiratory muscles, isolated ocular form [4-6].

One of the characteristic features of anti-MuSK MG is the presence of atrophy and fatty infiltration of the tongue, extraocular, mimic, masticatory and paravertebral muscles, detected by MRI and proton magnetic resonance spectroscopy (MRS) [5,7-11]. This feature presents as a consequence of myopathic process in anti-MuSK antibody MG, which is confirmed by changes in the myopathic EMG pattern in 44-50% of cases. Those changes include a decrease in the MUAP durations, amplitudes and the presence of fibrillation potentials [3,7,12,13]. Muscle atrophy is more common in patients with longer disease course [7,8]. However, some cases of anti-MuSK MG were reported with a short course, characterized by the presence of neurogenic changes in the muscles [14-16]. In the studies of experimental autoimmune MG in mice, a wide range of evidence was obtained in favor of denervation changes in muscles in anti-MuSK MG [17-19]. At the same time, in humans, in most muscular morphological studies of the extremities, predominant myopathic [20-23] and rarer presynaptic neurogenic changes were observed [19]. Thus, the exact nature of muscle damage in patients with anti-MuSK MG remains debated. The question is of importance since myogenic changes are less susceptible to respond to a therapeutic intervention.

In this article, we report reversible probably neurogenic changes, identified by nerve conduction studies (NCS), repetitive nerve stimulation (RNS), electromyography (EMG) and MRI, in paravertebral muscles in two patients with anti-MuSK antibody MG.

Subjects and methods

The examination and treatment of two patients: K. 51-year-old male and P. 44-year-old female with paraspinal-muscle weakness caused by anti-MuSK MG were carried out. The clinical, neurological examination and the quantitative myasthenia gravis score (QMGS) assessment were performed before and after the therapy.

All studies were conducted after the patients had signed the voluntary informed consent.

Laboratory methods included: general, biochemical blood analysis, determination of IgM, IgG and IgA levels (turbidimetric method, BTS-350, BioSystems, Spain), antibodies to antinuclear factor (ANF) by indirect immunofluorescence (iIF) test (Euroimmun, Germany), extractable nuclear antigen (ENA) by ELISA (Orgentec , Germany), anti-MuSK antibodies by ELISA (IBL, Germany), anti-AChR antibody test by ELISA (Medipan, Germany), anti-skeletal muscle antibodies (anti-SM) by iIF (Euroimmun, Germany), myositis-associated antibody test (MAA) (Mi2b, Ku, Pm-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12 EJ, OJ, Ro-52) (Euroimmun, Germany).

Instrumental methods consisted of: nerve conduction studies (NCS), repetitive nerve stimulation (RNS) (rhythmic stimulation 3 and 50 Hz), needle electromyography (EMG), whole-body MRI using T1-weighted, T2-weighted STIR-T2 weighted sequences in three orthogonal orientations (Philips Ingenia 1.5 Tl), chest CT (Aquilon 64, Toshiba).

Treatment of patient 2. (44 y.o.) included methylprednisolone tablets (0.8 mg/kg b.w.) by an alternating scheme and five cycles of medium-volume membrane plasma exchange using PCS-2 devices (Haemonetics, USA) according to the standard technique with an exfusion volume of 25-30% of the circulating plasma volume. The replacement of the exfused plasma was carried out with crystalloid solutions. Patient 1 (51 y.o.) received only methylprednisolone tablets (1.0 mg/kg b.w.) according to an alternating scheme. In both patients, when the methylprednisolone doses were decreased, azathioprine tablets (50 mg/day) were additionally prescribed.

Description of clinical cases

Patient 1 (male, 51 years old; 186 cm tall, weighting 79 kg; BMI - 22.8) presented with a 8-month disease duration. He complained of severe muscle weakness of the back and neck, with difficulties to maintain the head and posture, inability to extend the back from a forward bend. After 2 months, the patient noted the appearance of double vision. The severity of symptoms had no significant fluctuations during the day. The neurological examination before treatment revealed moderate weakness of the neck extensors (4 points) and severe weakness of the thoracic and lumbar paravertebral muscles (3 points). When the arms were extended forward, a compensatory deviation backward of the body by 10° was observed. Weakness in the facial and proximal muscles of the upper limbs was not observed (5 points). The QMGS score was 3/39 points. The patient was MGFA class 1. The neostigmine methyl sulfate test (0.05% 2 ml) was positive.

The level of anti-AChR antibodies were 0.24 nmol/L (norm of up to 0.45); anti-MuSK antibodies were more than 23.3 IU/ml (norm of up to 0.39 IU/ml); anti-SM antibodies - less than 1:20 (up to 1:20); ANF antibodies were 1: 640; anti-mitochondrial antibodies (PDC-AMA2; AMA) - 1:20 (less than 1:20); immunoblotting of antinuclear antibodies was normal. The IgM, IgG and IgA levels were normal.

On the whole-body MRI in m. multifidus at levels Th10 - L5 MR signal was heterogeneous, particularly on the left side due to areas of moderate hyperintensities on T2w images, with corresponding iso/hypointensities on

Table I. Results of RNS, assessment by QMGS and anti-MuSK level of patient 1 and patient 2 before and after treatment.

Muscles	Patient 1 (51 y.o.)				Patient 2 (44 y.o.)			
	Before	After	Before	After	Before	After	Before	After
	A, mV	D, %	A, mV	D, %	A, mV	D, %	A, mV	D, %
M. frontalis	**1.1**	6.5	1.6	0.5	**1.1**	**20.4**	1.5	**12.4**
M. orbicularis oculi	2.4	**23**	2.5	+ 0.2	**0.45**	**38.4**	**0.99**	**34.2**
M. nasalis	2.8	8.6	2.7	2.5	1.81	**25.4**	2.62	3.8
M. digastricus vent. anterior	4.7	1.5	5.1	+ 0.8	3.61	**18.6**	6.78	+ 0.6
M. trapezius	5.6	**65**	11.9	**13.1**	6.85	**17.1**	10.1	1.9
M. deltoideus	20	**19.3**	25.7	5.7	12.8	**16.8**	19.1	2.6
M. abductor digiti minimi	14.1	2.4	14.0	+ 0.4	9.4	2.4	10.3	+ 0.9
PAP (m. orbicularis oculi), %	112		108		127		123	
Anti-MuSK antibodies, IU/ml	23.3		8.13		25.3		7.26	
QMGS	3		0		17		1	

A, mV: amplitude of the first CMAP; D,%: decrement in the amplitude of CMAP between the first and fifth stimuli, expressed as a percentage, obtained with repetitive stimulation of 3 Hz; PAP: Post-activation potentiation after isometric muscle tension; 4: Pathological indicators are highlighted in bold.

T1w images. Those areas showed edematous changes. No signal anomaly was detected elsewhere, either in the paravertebral muscles or in the paravertebral soft tissues at other locations.

A L5-S1 disc protrusion was observed, up to 0.35 cm in size, without affection on the spinal roots. In the posterior group of thigh and leg muscles, mild fatty replacement was noted (Mercuri 1 grade 1 on a scale of 0 to 4).

Respiratory function indices were in the normal range.

On the repetitive nerve stimulation compound muscle action potentials (CMAP) decrement was revealed in the orbicularis oculi muscles (23%) and the proximal muscles of the upper extremities up to 65% (Tab. I). On the EMG in m. deltoideus, m. vastus lateralis, m. tibialis anterior, the MUAP amplitudes and durations were normal. In the proximal muscles increased polyphasia of MUAP was noted up to 26-33%. In m. erector spinae at the L1-L3 levels, neurogenic changes were revealed, represented by an increase in the MUAP amplitudes - 1814 μV (343-4172 μV), with a normal MUAP duration - 11.1 ms (8.43-16.4), an increase in polyphasic fibers up to 14%; the interference pattern corresponded to the neurogenic one. Spontaneous activity was represented by the multiple fibrillation potentials, positive sharp waves and single fasciculations.

After treatment, which included glucocorticosteroids (1.0 mg/kg b.w.in an alternate day scheme for 4 months, followed by a progressive decrease), patient 1 achieved complete clinical remission.

A control examination after 6 months of therapy showed a decrease in the anti-MuSK level to 8.13 IU/ml. At the MRI, the complete regression of edematous changes in the paravertebral muscles was observed (Fig. 1). On the RNS, the CMAP decrement in m. trapezius persisted. In m. erector spinae at the L1-L3 levels, less pronounced neurogenic changes were observed, indicated by lower MUAP amplitudes - 1610 μV (567-2942 μV), with a normal MUAP duration of 10.5 ms (9.07-14.6), an increase in polyphase fibers to 32%. The interference pattern corresponded to a neurogenic one. QMGS score - 0/39 points. The patient 1 was MGFA class 0 (Tab. I).

Patient 2 (female, 44 years old, height 166 cm; weight 68 kg; BMI - 24.7) with complaints of double vision, limitation of eye movements, the drooping eyelids and rapid fatigability of the neck extensors with the development of "dropped head" syndrome in the evening. The first episode of self-regressing isolated double vision, which lasted 2 weeks was observed 8 months ago. Ophthalmoparesis was observed within 4 months. On examination before the treatment, diplopia, ophthalmoparesis, convergent strabismus, hypomimia, weakness in the neck extensors were noted. She could not raise her head in a forward tilt position (2 - 3/5 points); she had weakness in the back extensors of the thoracic and lumbar regions (4 points). Muscle strength of the upper and lower extremities was normal (5 points). QMGS score - 17/39 points. The patient 2 was stage 2a according to MGFA. The neostigmine methyl sulfate test (0.05% 1.8 ml) was positive (Fig. 1).

The level of anti-AChR antibodies was 0.21 nmol/L (normal up to 0.45); antibodies to MuSK more than 25 IU/ml (norms up to 0.39 U/ml); anti-SM antibodies - less than 1:20 (the norm is up to 1:20). Blood cell count showed a relative lymphocytosis of up to 47.4% (norm 19.0-37.0%) with normal absolute lymphocyte number.

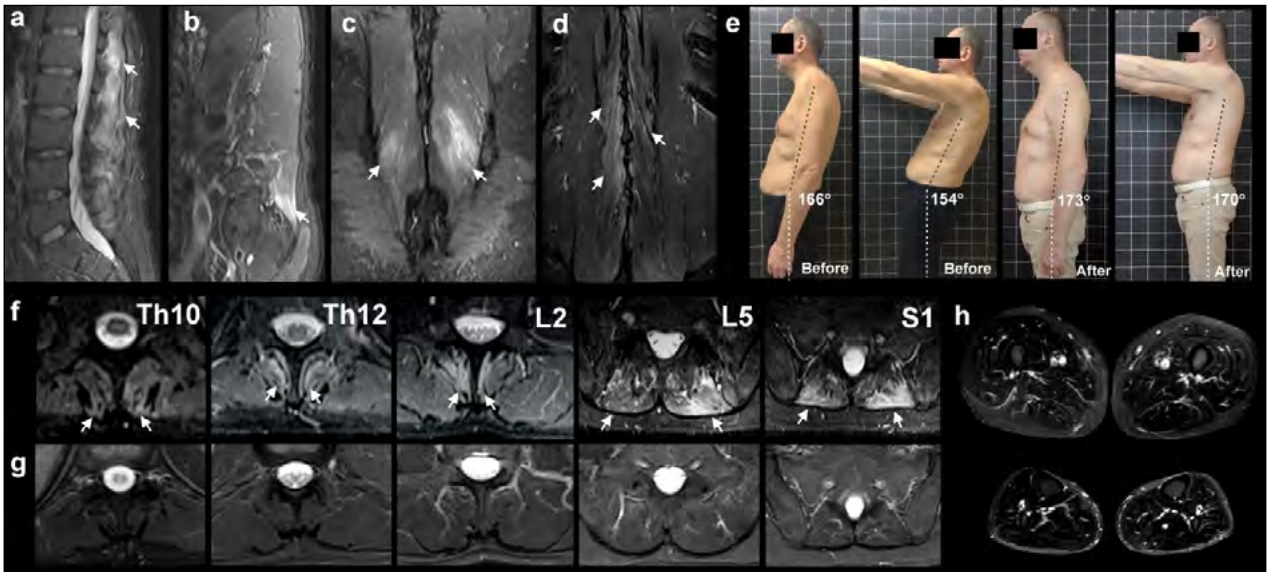

Figure 1. Patient 1, 51 (y.o.), with anti-MuSK MG had a disease duration of 5 months. There is edema of m. multifidus on STIR in the sagittal plane (A, B), in the coronal plane (C, D). Muscle weakness of the back extensors has been presented as a compensatory deviation of the trunk back when raising the arms up before and after treatment (E); edema of m. multifidus and m. erector spinae before and after therapy (F, G) on STIR in the axial plane; no pathological changes in the muscles of the thighs and lower legs on STIR in the axial plane (H), the pathological changes are marked with white arrows.

On chest CT persistence of the thymus gland was revealed (7.6x11 mm, no clear contours).

At MRI, whole-body axial STIR and T2wi in the axial plane revealed the moderate edematous changes in m. multifidus at the Th12, L3-L5 levels, m. erector spinae at the L4, L5 levels on the left (Fig. 2A). On the T1w and T2w scans in sagittal, coronal and axial projections with fat suppression, the patient had protrusions of the L3-L5 intervertebral discs measuring 0.2-0.3 cm, without signs of nerve root compression. In the STIR and T2w images of extraocular muscles, moderate symmetric edematous changes in m. rectus lateralis and m. rectus inferior were observed in the absence of structural pathological changes on T1wi. The tongue did not reveal any pathological edematous change or pronounced fatty infiltration (Fig. 2I).

Respiratory function indices corresponded to the norm.

The RNS (rhythmic stimulation 3 Hz) revealed a M-response decrement in the mimic, pharyngeal and the proximal muscles of the upper extremities by 38% (Tab. I). The EMG in m. deltoideus, m. vastus lateralis, m. tibialis anterior showed normal values of the MUAP amplitudes and durations while the MUAP polyphasia in the proximal muscles was increased up to 23-40%. In the m. erector spinae at the L2-L4 levels, neurogenic changes were revealed, represented by the increased MUAP amplitudes - 1514 μV (292-3802 μV), with a normal MUAP duration - 11.9 ms (8.43-16.4), polyphase fibers - 9%; the interference patterns corresponded to the neurogenic one. Signs of spontaneous activities included multiple fibrillation potentials, single fasciculations, and positive sharp waves. The number of fasciculations prevailed on the left side where MRI identified more pronounced edematous changes.

After a 2-month treatment, which consisted of glucocorticosteroids (0.8 mg/kg b.w.) administered each other day and five medium-volume plasma exchanges, patient 1 reached a complete clinical remission. Methylprednisolone-dose was then gradually reduced and azathioprine (50 mg/day) was added.

A follow-up study 3 months after had been initiated showed the decreasing anti-MuSK antibodies to 7.26 IU/ml. A complete regression of the paravertebral muscles edematous changes was seen at the MRI, but a moderate edema still persisted in m. rectus inferior. On the RNS, the elevated CMAP decrement in m. orbicularis oculi persisted. The MUAP parameters of the paravertebral muscle were in the normal range. No spontaneous activity was detected, but the MUAP polyphasia remained up to 34%. QMGS score was 1/39 point (Fig. 1). The patient 2 was MGFA class 0.

Discussion

The first clinical case was a rare example of an-

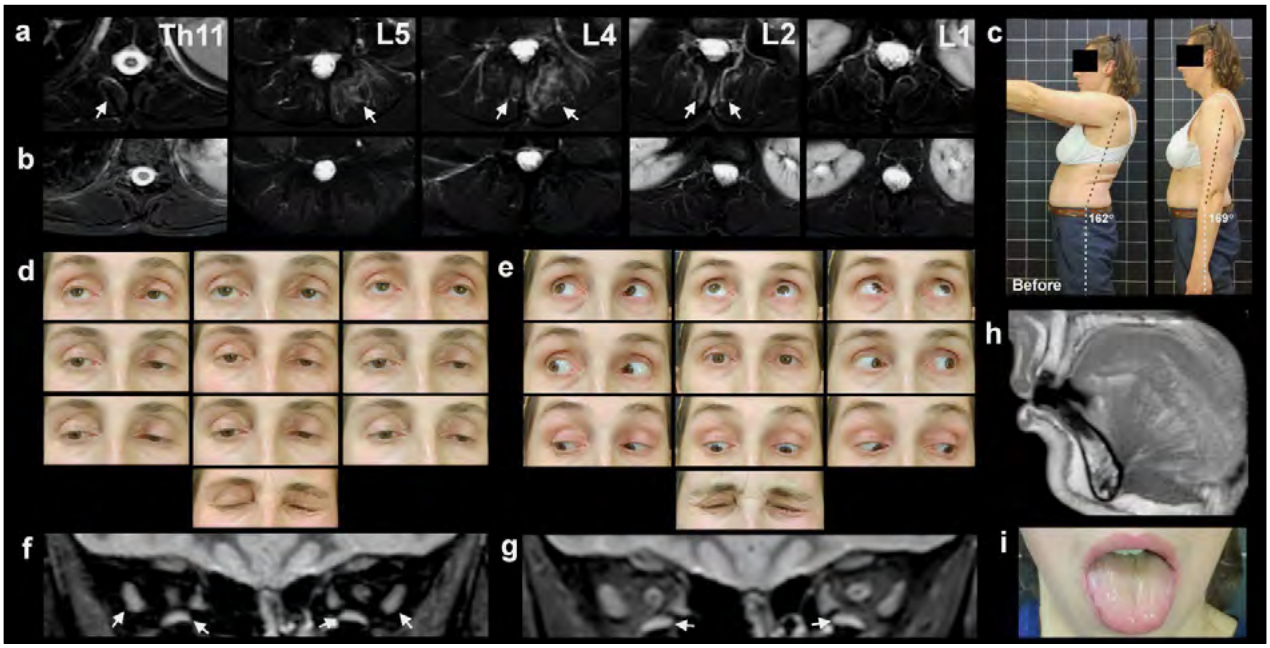

Figure 2. Patient 2 (44 y.o.) had anti-MuSK myasthenia gravis with a 7-month disease duration. Edema of m. multifidus was on STIR in the axial plane at the Th11-L1 levels before the treatment (A) and after the therapy (B). There was no significant deviation of the trunk when raising the arms up in the presence of moderate weakness in the back extensors (C). Weakness of the extraocular muscles. The motion range of the eyes before (D) and after the therapy (E); edemas of m. rectus lateralis and m. rectus inferior before the therapy (F), m. rectus inferior after the therapy (G) on STIR in the coronal plane; absence of significant fatty infiltration in the tongue muscle according to T1-WI in the sagittal plane (H); appearance of patient's tongue (I) (pathological changes are indicated by arrows).

ti-MuSK myasthenia gravis, manifested with an isolated lesion of the paravertebral muscles, predominantly of the lower thoracic and lumbosacral regions. That lesion included the pronounced difficulties in extending the trunk from bending forward and maintaining balance with arms extended forward. Previously, cases of primary involvement of the paravertebral muscles were described only in children (7 years). They were accompanied by the developing scoliosis and atrophy of these muscles at the cervical and thoracic levels [11,24]. In both cases, the scoliotic deformity significantly decreased after treatment. The second case was characterized by a milder involvement of the axial muscles than in the first case. In particular, there was a moderate "dropped head" syndrome in the evening and mild involvement of the lower thoracic and lumbar paraspinal muscles, manifested by lumbar fatigue when standing. As it is known, the axial muscles are often involved at the cervical levels with the development of "dropped head" syndrome in patients with anti-MuSK MG [14,25-28], and even more often in patients over 60 years old with anti-AChR antibodies in 10% of cases [29,30], while in other anti-AChR patients, the lesion of the neck flexors prevails [31].

In both cases, primary involvement of the axial musculature prompted a whole-body MRI scan to rule out myopathies. Unexpected edematous asymmetric changes in the paravertebral muscles were revealed. These changes were more pronounced in the first patient (the MR signal hyperintensity on STIR, T2-WI, iso/hypointensity on T1-wi) in m. multifidus at the Th10-L5 levels and m. erector spine at the level of L5-S1 segments. Signal hyperintensity on STIR in combination with spontaneous activity on EMG characterizes muscle denervation in the acute (up to 1 month) and subacute phases (1-6 months) [32,33]. Such changes are due to the expansion of the capillary bed and the increasing intercellular fluids [34], already developing 48 hours after denervation [35]. Similar changes can be observed not only during denervation, but also during primary muscle inflammatory processes, including inflammatory myopathies [36]. In both our cases, the presence of inflammatory myopathies was ruled out by normal level of CPK, AST, ALT, LDH, and myoglobin, as well as negative results of the myositis-associated and antimitochondrial antibodies. A STIR positivity at MRI has a sufficiently high relative sensitivity - 84% and specificity - 100% for detecting denervation (acute and subacute phases) when compared with EMG [37,38]. In chronic phase (more than 6 months), an increase in muscle fat content and muscle atrophy are observed, which is accompanied

by the development of the MR signal intensity on T1wi and a decrease in muscle mass. Similar changes are also observed in functional immobilization (for example, tendon rupture) and hereditary muscular dystrophies [32,33].

In most of the previously reported cases of anti-MuSK [24] and anti-AChR [39,40] MG, associated with the axial muscle damage ("dropped head" syndrome, camptocormia), the MR signs of fatty infiltration and paravertebral muscle atrophy were described even with or without the glucocorticosteroid therapy. In patients with anti-AChR MG, a summation of similar MR-changes, the "myopathic" EMG patterns in paraspinal muscles and resistant camptocormia has been stated by a number of authors as an independent rare comorbid condition – "paraspinal myopathy" [41,42]. Similar cases of the anti-AChR MG and "paraspinal myopathy" were described in patients aged 70-85 years with a long course and poor control of MG symptoms. The presence of cases of reversible camptocormia, "dropped head" or "Leaning Tower of Pisa" syndrome during the treatment in patients with anti-AChR and anti-MuSK MG who have myopathic EMG signs with or without atrophy, but without fatty infiltration of the paravertebral muscles, probably indicates that the damage to this muscle group is one manifestation of myasthenia gravis [43-45]. Thus, myasthenic weakness, leading to functional immobilization of the paravertebral muscles, probably determines the stage process of their affection. Initially, the development of early edematous changes is the same as for the acute and subacute phases of denervation, which corresponds to our cases. Subsequently, late changes, equivalent to chronic denervation, which corresponds to most of the previously described cases [41,42]. This correlation indicates that the presence of the paravertebral-muscle lesion with anti-MuSK MG can lead to scoliotic deformity in childhood. At the same time in elderly patients with anti-MuSK, as well as anti-AChR MG, the paraspinal damages may cause camptocormia and "dropped head "syndrome.

The muscle MRI characteristics of the limbs in patients we described corresponded to the control muscles. The only exception was minimal signs of fatty infiltration in the lower extremities (grade 1 according to Mercuri), which was probably a consequence of a sedentary lifestyle [46].

Besides, in two patients, there were no edematous changes, fatty infiltration and atrophy of the tongue, mimic and masticatory muscles, probably due to short disease duration (4-6 months). These findings contradicted the typical signs of anti-MuSK MG, which were atrophy and fatty infiltration of m. orbicularis oculi, m. orbicularis oris, m. buccinators, tongue muscles [8], mm. pterygoidei, m. masseter and m. temporalis [9]. In some cases, atrophy of the tongue muscles is reversible [24,47]. The severity of atrophy and fatty infiltration depends on the duration of prednisolone therapy [8]. However, in some cases, atrophies developed at an early stage even before the initiation of the treatment, which was most likely due to the independent role of anti-MuSK in this process [9,48]. In particular, Punga, et al. (2011) showed that MuSK antibodies induced functional denervation, resulting in increased production of the skeletal-muscle-atrophy marker MuRF-1 (atrophy marker muscle-specific RING finger protein 1) [49] in a passively induced model of experimental autoimmune MG in mice [18,50]. At the same time, a significantly greater increase in mRNA levels of MuRF-1 was observed in the masticatory muscles, while those levels decreased in the limb muscles (m. soleus). These findings explained the peculiarities of the atrophy distribution in anti-MuSK MG [18,50]. The progression of atrophy under the anti-MuSK influence was also realized through overexpression of atrogin-1 and p21, which provoked a premature stop of the cell cycle and weakened the ability of satellite cells to replace lost muscle fibers [18,51,52].

Similar regularities were observed in the MR changes of the oculomotor muscles in anti-MuSK MG. Thus, in our second case, severe ophthalmoplegia lasting 4 months was characterized by moderate edematous changes (according to STIR) in m. rectus lateralis and m. rectus inferior, which corresponded to MR signs of early functional denervation. Whereas in cases of prolonged ophthalmoparesis (2-14 years) with anti-MuSK MG, the MR signs of pronounced atrophy in extraocular muscles were observed [5,6]. In these cases, the least affected muscle was m. obliquus inferior.

Thus, muscular atrophy, especially of the mimic and bulbar muscles, has been a fairly common delayed consequence of anti-MuSK MG, reflecting the disease duration, the delayed initiation of therapy and/or the effect of prolonged exposure to high doses of glucocorticosteroids [53]. The intricacy of mechanisms is supported by the variability of the prevalence of atrophy in anti-MuSK MG, from 5.7 [54] to 23% [7]. The assessment of muscle condition by MRI at the time of diagnosis is a important to estimate the possible functional recovery under therapy [6,9].

The CMAP decrement with RNS of 3 Hz was revealed in both clinical cases, while the decrement curve had a steadily progressive character, in contrast to the U-shaped form in anti-AChR MG [55]. In both cases, there was no hypercholinergic reaction after the first supramaximal stimuli that performed with additional potentials after the M-response [56]. This result may be due to the short duration of the disease and the low doses of acetylcholinesterase inhibitor (AChEI) used (up to 180 mg/day of pyridostigmine bromide). In the first case, the decrement distribution of the examined muscles mainly reflected the focal nature of the lesion with maximum values of the

CMAP decrement up to 65% in m. trapezius. Whereas the second case was clinically similar to the generalized form of anti-AChR, characterized by a more diffuse distribution of the M-response decrement. The maximum values of the CMAP decrement corresponded to those values in the most affected muscle groups. The significant variability in the decrement distribution in anti-MuSK MG substantiated the rationality of more extended studies. At the same time, the diagnostic significance increased from 56.8 [22] to 85% when the neuromuscular-conduction analysis included not only distal, but also proximal muscles of the extremities, as well as facial muscles [28,54,57].

Needle EMG was performed to determine the neurogenic nature of the hyperintense-signal areas (on STIR) of the paravertebral muscles. Paraspinal MUAPs had increased amplitudes and normal durations with a slightly increased polyphasia up to 14%. Whereas in the limb muscles without MR lesion signs, duration and amplitude MUAPs were normal, albeit with a significantly increased polyphasia up to 40%. Spontaneous activity was only detected in the STIR hyperintense areas in the paravertebral muscles and represented by a significant number of fibrillation potentials, positive sharp waves, and single fasciculation potentials. On turn-amplitude analysis, a neurogenic pattern of the interference curve was observed in the paravertebral muscles, characterized by a high amplitude with a reduced or normal frequency of turns. In both cases after the therapy, the MUAPs almost completely returned to normal. However, in most studies of anti-MuSK patients, the myopathic nature of EMG changes was reported: a decrease in the MUAP durations and amplitudes, the presence of fibrillation potentials [3,12,57]. Myopathic MUAPs were observed in 62-80.6% of anti-MuSK patients in facial muscles [7,12], although in limb muscles, they were in 33-44% [7,13]. It should be noted that the interpretation of MUAP changes in anti-MuSK and anti-AChR is questionable, when different stages of the denervation process are not taken into account. In particular Farrugia, et al. (2007) indicated that in 50% of anti-MuSK patients with MUAP myopathic patterns in turn-amplitude analysis, the interference curve was characterized by high amplitudes and low frequency of turns [12]. This result was interpreted as an insufficient strength of studied-muscle contraction, and not a sign of early functional denervation [12].

In cases with predominant lesions of the paravertebral muscles, the myopathic nature of the MUAP changes was accompanied by muscle atrophy during a long disease course [11]. At the same time, cases with a short duration of anti-MuSK MG and axial-muscle damages were described, characterized by reduced duration of MUAPs, increased polyphasia and pronounced spontaneous activity (fibrillation potentials, fasciculations, positive sharp waves), which was regarded as neurogenic changes and was a cause of amyotrophic lateral sclerosis (ALS) misdiagnosis [14-16,24]. In some cases, EMG signs of fasciculations were accompanied by clinically evident fasciculations [16,58].

A similar nature of MUAP changes and the presence of spontaneous activity were described in studies of experimental autoimmune myasthenia gravis and in some clinical cases, in which denervation changes in the affected muscles were substantiated [18,19,21,59-65]. The degree of nerve penetration in each muscle has been shown to correlate with their endogenous MuSK levels [18,66].

Summing up the available data, in anti-MuSK myasthenia gravis, most researchers have considered these muscle damages as myopathic process [1,3,7,12,22]. Whereas our clinical examples have confirmed the presence of neurogenic changes at an early stage of anti-MuSK myasthenia gravis and indicated importance of immediate initiation of pathogenetic therapy to avoid the development of muscle atrophy and fatty infiltration.

Conflict of interest statement

The authors declare no conflict of interest.

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Author's contributions

The authors have contribuited equally to the work.

Ethical consideration

Not applicable.

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Neuromuscular disorders and transition from pediatric to adult care in a multidisciplinary perspective: a narrative review of the scientific evidence and current debate

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Objective. Standards of care and new genetic and molecular therapies have contributed to increasing life expectancy of patients with neuromuscular diseases (NMDs). This review presents the clinical evidence for an adequate transition from pediatric to adult care in patients with NMDs considering both physical and psychosocial aspects and attempts at identifying a general pattern of transition in the literature that can be used for all patients with NMDs. Method. A search was performed on PubMed, Embase and Scopus using generic terms that could be referred to the transition construct specifically related to NMDs. A narrative approach was used to summarise the available literature. Results. Our review shows that few or no studies explored the transition process from pediatric to adult care in neuromuscular diseases and tried to identify a general pattern of transition applicable to all NMDs. Conclusions. A transition process taking into consideration physical, psychological, social needs of patient and caregiver could produce positive outcomes. However, there is still no unanimous agreement in the literature on what it consists of and how to achieve an optimal and effective transition.

Key words: transition, neuromuscular disorders, psychological care, social care, healthcare

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Glossary

Transition: complex and gradual process, planned movement of young patients (starting at around the ages of 12 and 14) with chronic physical and medical conditions from child-centered to adult-oriented healthcare systems. Physical, psychological and social aspects of young patients and their caregivers are considered. It could have positive or negative outcomes on prognosis. It is an educational process.

Transfer: changing of adolescents or young adults with chronic physical or medical conditions from pediatric to adult care (owing to an event or series of events).

Transitional program: a series of multidisciplinary measures to prepare adolescents to take charge of their own situation.

Introduction

Neuromuscular disorders (NMDs) are a genetically and phenotypically heterogeneous group of diseases affecting the neuromuscular system, namely the anterior horn cell, the peripheral nerve, the neuromuscular junction, or the muscle itself. NMDs as a whole are not infrequent, but every single one of them is a rare or orphan disease (prevalence < 1 per 1,500 persons in the U.S. and < 1 per 2,000 persons in Europe). Their causes can be genetic (single gene disorder, polygenic disorder) or nongenetic (infectious, autoimmune, autoinflammatory) [1,2]. Clinically, the vast majority of NMDs are progressive, impairing motor function and often reducing life expectancy as well as quality of life. Age of disease onset varies. Some diseases are genetically inherited while others manifest in childhood or have an adult onset. For many decades, treatment of NMDs has been exclusively symptomatic but in recent years new genetic and molecular therapies and other focused on pathogenic effects are available or under development, provide hope for mitigating secondary pathophysiological consequences or modifying the underlying genetic defect [3-5]. NMDs need to be treated as systematic diseases due to increased life expectancy resulting from comprehensive standards of care involving multidisciplinary and coordinated care and new therapeutic methods. For this reason, it is possible to witness an expansion of the phenotypic manifestations of the disease with new or previously subtle organ manifestations [6].

NMDs should be approached from a multiple perspective. For example, spinal muscular atrophies (SMAs) are a group of NMDs characterized by alpha motor neuron degeneration in the spinal cord, resulting in muscle atrophy, weakness and paralysis [7,8]. Given their complexity, a multidimensional approach to the management of SMA is required, and no aspects should be treated independently, such as social and psychological care [8]. Along the same line, Duchenne muscular dystrophy (DMD) – caused by mutations in the dystrophin gene resulting in complete absence or low levels of dystrophin protein [9] – should include a focus on mental and social health. In this multidimensional approach, issues related to transition from pediatric to adult care cannot be overlooked, just because the chances of survival have increased [10]. As reported by Goselink and colleagues [11] transition is the process started by physicians to prepare the child or young adult and their family for transfer from pediatric to adult care. Nonetheless, even though progress in health care has increased life expectancy, support at home and in the community has not increased [12].

Transition should be carefully planned. Inadequately planned and gross transition processes could lead to negative outcomes related to mortality, prognosis, psychosocial and educational well-being [13,14]. All transition processes should be tailored specifically [15].

This paper presents a review on transition from child to adult care to illustrate the importance of an adequate transition process covering all aspects of NMDs. It highlights the clinical evidence and discusses the psychosocial implications underlying positive outcomes in the transition process from pediatric to adult care for patients with neuromuscular diseases. An attempt is made to identify a possible "standardized" protocol that could be used in all patients with neuromuscular conditions.

Towards a definition

Transition is "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health-care systems" [16]. Several definitions of transition can be found in the literature. For example, Moons et colleagues [17] distinguish between transition, transfer or transitional care. Transition is the passage from one phase of a person's life, physical condition or social role to another. It is also characterized by different stages, milestones, and turning points, and can be defined through process and/or terminal outcomes [18]. It could be considered an educational process that should begin before children reach adolescence [19]. Transfer is the passage from pediatric to adult care of an adolescent or young adult with chronic physical or medical conditions. Transitional care is the set of medical, social, psychological, educational and professional measures to prepare adolescents to take responsibility for their situation.

It is a crucial process that needs to be accurately planned to support families in the process and health care providers to define an appropriate transition plan [20,21].

The two terms – transition and transfer – cannot be used interchangeably. As reported by Tilton [22], transition is an extended and complex process that begins in early adolescence and offers a staged and gradual assessment of readiness as well as resources and education. Sawicki et colleagues [23] developed a useful tool for assessing readiness of youth with special healthcare needs.

To avoid worsening health conditions and lack of interest in services, it is necessary to bridge the gap between services for adults and children by identifying the key aspects of transition programs in a multidimensional perspective [24]. The transition process should begin quite early, at around the age of 12 or 14, and should aim to progressively increase a person's autonomy [25-27]. It does

not end when the adolescent moves to adult-oriented care. In fact, it should be considered as an opportunity to rethink diagnosis and management. In addition, adolescents should undergo psychosocial screening before and after moving to adult-oriented care [28].

Aho and colleagues [29] highlight how transition from childhood to adult age is an important phase because patients start to perceive the need to understand their life and make their life understood by the others. In addition, patients need to know what coping resources are available and give meaning to life. Therefore, support provided by health care professionals for future management of their disease becomes important.

Transition as a process does not involve solely young patients but also their parents. For example, individual or group psychological interventions could reduce their anxiety and worry about their children [30]. Family involvement is important for a successful transition of youth with disabilities [31,32].

Methods

This review specifically focuses on transition for young patients with NMDs. The aim is to identify a "standardized" transition protocol that can be used with all young patients with NMDs. Given the small number of papers available on transition as a unique and non-pathology-specific construct, we opted for a narrative approach vs a systematic review. As reported in the literature [33,34], there are no recognized guidelines for narrative reviews. A narrative review should however have a structured general framework (rationale, organization of collected information, definition of objectives and goals) and follow a methodology in literature search (database, keywords, inclusion and exclusion criteria, list of references used). It could include a systematic review methodology, but this is not a necessary element. It may or may not include comprehensive search and/or quality assessment, and analysis may be chronological, conceptual, thematic, etc. It could be a good way for identifying omission or gaps [34].

A search was performed on PubMed, EMBASE, and Scopus using generic terms that could refer to the transition construct for NMDs. Keywords such as Duchenne muscular dystrophy (DMD) or spinal muscular atrophy (SMA), etc. were not included because we were looking for broadly adaptable references to different forms of neuromuscular diseases. Hence, we searched for terms such as "transition", "neuromuscular diseases", "neuromuscular disorders", "transition process". Non-English language studies and works were excluded. Only papers containing the selected keywords in the title and/or abstract were considered for further analysis. No chronological criteria were applied.

Thirteen articles were selected that specifically reflect the aforementioned criteria. Most of them try to deal with and deepen both the purely physical and the psychosocial (and sometimes ethical) aspects in the transition processes in NMDs. However, only a few try to identify a model applicable to multiple NMDs.

Supplementary Table I reports the main articles containing the selected keywords in the title and/or in the abstract. It shows the aims and main topics of each article. Moreover, through an analysis of the entire text of each article, they were screened according to the topic of this review.

Results

Neuromuscular disorders and transition process

Interest in transition from pediatric to adult care in NMDs is increasing. Key aspect do not only include medical care but also psychological and social aspects, and increased survival requires rethinking educational, social and psychological services. For a successful transition and care, integration of wider social issues, involvement of young patients and their families in decision-making, support of patient advocacy groups, and proactive care are not to be overlooked [35,36]. To improve patient outcomes, an extensive transition program should focus on the patient's physical, psychological and social development and not only plan physical transfer from pediatric to adult care [37]. However, particular attention should be paid to the needs and requirements of a wide range of people with different and more or less debilitating conditions in order to avoid negative outcomes. Involving adolescents in planning transition could be a good strategy. For example, a key aspect is independence and it should be determined whether is a goal to be pursued or not [15]. For a young patient with a progressive neuromuscular disease, transition could be an intense period (both from a psychological and physical perspective) in which skills could be lost and dependence on others increases [38]. Furthermore, understanding the personal characteristics as well as the needs and aspirations of young people could help provide the right health care [39].

The perspectives and needs of patients with NMDs should not be underestimated. Young people with NMDs report a similar view in the different forms of diseases, of the transition process. Care during transition should be consistent and tailored to the individual's needs [10,40]; access to a wide range of information should be guaranteed. The process should be gradual and timed and should include peer support programs [41]. Therefore, mental and social health is a crucial aspect of the process.

Family members need to be involved in planning. This allows professionals to make choices in line with

their needs and values, involve them in decision-making and provide adequate information in the right ways [38].

From a physical point of view, it is necessary to consider the progression of many signs and symptoms. For example, progressive muscle weakness as the main manifestation of DMD may become exacerbated in adult age owing to a lack of adequate and regular physical activity [42]. Therefore, a multidisciplinary rehabilitation assessment with interventions across all disease stages is recommended [9,42,43]. Respiratory problems are another example. All or almost all therapies for respiratory management (e.g. monitoring of respiratory muscle function and the timely use of lung volume recruitment, assisted coughing, nocturnally assisted ventilation, and subsequent daytime ventilation) should be used even before transition from pediatric to adult care providers [44].

Health and physical care

For patients with NMDs, transition from pediatric to adult care is a critical phase. Key findings suggest that this process remains problematic with a gap between pediatric and adult care services, including significant differences in clinical practice and culture with a tendency for the adult physician to focus more on specific medical aspects as opposed to a global, interdisciplinary view. The transition process should ensure a plan for ensuring continuity of care with pediatricians [10].

The pediatric team should initiate the process gradually by educating patient and caregiver, identifying the practitioner in charge, updating key management plans, addressing key problem areas, and assessing readiness to transfer at each visit [45]. An up-to-date and accessible medical record may be useful and help the team to collaborate actively and jointly [46].

Monitoring patients with chronic conditions allows to observe recurring themes present and relevant in most NMDs, attributed to the specific muscle or nerve disease and its effect on other areas of the body [47].

Brown and colleagues [26] suggest that young patients and their caregivers should be involved in transition planning (at least once a year) through scheduled visits starting from age 13. Indeed, as mentioned above, the recommended age for an effective transition is between 12 and 14 years old [25-27]. These visits should address: the young person's medical condition; current medications and any side effects; genetic counseling and reproductive implications of the condition; issues related to sexuality and puberty; psychological well-being; any additional tests or assessments to be performed prior to transfer; a current assessment of the young person's understanding of his/her diagnosis and prognosis (if with severe cognitive impairment, plans are established for legal guardianship). Physicians should provide transparent information and guidance to patients on the management of the terminal phase of NMDs, too. But often this type of communication occurs at a late stage [48].

During adolescence, therefore, transition from childhood to adulthood, symptoms and signs may progress. For this reason, rehabilitation or support should be provided. The main areas of intervention may concern the muscular and skeletal system, the respiratory system, cardiological aspects and consequences, gastrointestinal and nutritional problems, the endocrine system, kidneys problems, orthopedic problems [42,43,49-55]. Patients with NMDs should attend follow-up visits on a regular basis, otherwise their risk of developing complications typical of NMDs or of their progression increases.

Emergency care planning is another key component of transition. Appropriate and timely interdisciplinary emergency management is critical for survival in these patients. Emergency cards (ECs) are provided for this purpose to patients and caregivers as a way to ensure timely and appropriate relief for these patients with unique and complex medical needs [56].

Obviously, then, transition from pediatric to adult care in patients with NMDs is complex and requires effective organization and planning.

Patients and caregivers: psychological care and implications

For a successful and useful transition from pediatric to adult care, psychological aspects in neuromuscular diseases should not be underestimated. For example, patients with SMA often experience anxiety, depression, and social isolation in response to increased symptom-related stress. However, mental health remains one of the unmet needs [7,57].

A high prevalence of depression and anxiety was found among school-age patients (age 8-18 years) with SMA and other muscular disorders. Prevalence seems to differ across school types, academic delay, household SES, clinical characteristics of disease, caregivers' mental health and expectations. No gender-related differences emerged [58,59]. This confirms once more the importance of making the transition process consistent with the young patient's needs and their family's.

With regard to dystrophies, it has been suggested that dysfunctions in dysbindin due to alterations in dystrophin could increase the risk of depression [60,61]. Some studies point to an increased incidence of anxiety and obsessive-compulsive disorder among children and adolescents with DMD [62-64]. Other emotional, affective and behavioural disorders, such as aggression, may also be present [65,66]. Physical symptoms may increase stress, especially in DMD vs Becker muscular dystrophy (BMD), the latter causing a less severe physical impairment [67].

Affective disorders should not be regarded as secondary conditions because they are not caused by mental retardation or physical disability. Furthermore, environmental and/or social factors, such as bullying, can affect mental health in NMDs [68,69].

Families often do not know what to do during the transition process, and young patients sometimes avoid telling their families how they feel about their disease or try to hide them to protect their parents [12,70]. Parents, on their part, feel useless or hopeless, which interferes with daily life. This may increase the risk of a major depressive episode [71]. Erby and colleagues [72] highlight that parents are afraid to explain the terminal nature of the disease to their children, and these fears could impact communication within families about care planning issues.

Because of the limited nature of screening, regular mental health assessments ensure continuity of care and provide longitudinal measures of the psychological state of the patient and families [73]. As previously reported, caregivers may experience stress as well as emotional and physical burden. One study reported more than fifteen components of caregivers burden, including stress, pain, anxiety, depression, sleep quality, and sexual function [74].

In addition, periodic neuropsychological assessments are advisable. There may be a correlation between molecular defects in genes mainly responsible for muscle diseases and cognitive impairment or between neurological findings and intellectual disability [75]. Therefore, active collaboration between professionals, patients and caregivers is necessary to ensure optimal transition in this critical period.

Social care and implications

The importance of social skills and social support during transition processes is an understudied topic in the literature. A combination of psychoeducational, psychosocial, relationship-centered, family-based education, support, communication, problem solving, and skills development interventions is recommended [76]. It appears that poor social and interpersonal behavioural skills are more significant than an increase in depressive and anxious behaviorus in boys with DMD [77]. In the same study, many boys with DMD display relevant social problems, such as poor peer relationships and immaturity. Furthermore, patients with NMDs could experience an important change in their social relationships, characterized by feelings of loneliness and isolation [78].

Especially adolescents express the need for meaningful relationships with professionals, family and friends looking for greater support in daily life [79].

Children with NMDs may show a particular behavioral phenotype with difficulties in social interaction and communication and probable issues in theory of mind [80]. DMD and BMD boys appear to have a higher level of social and communication difficulties compared with children with other muscular disorders or with the general population [81].

Poor social support could lead to problematic behaviours. As reported by Fee and Hinton [82], problematic behaviours decrease with increased social involvement, which acts as a protective factor and also leads to a reduction in internalizing problems. Social closeness with peers with similar life experiences can enhance the physical and psychological well-being of young people with NMDs (or, in general, with disabilities) [83].

Finally, turning to the needs of young people, information on more intimate aspects should be collected, including desire for intimacy, sexuality and family planning. In point of fact, the need to explore one's identity arises in adolescence, but it becomes manifest above in early adulthood, when individuals start to think how to structure their life – both private and professional [84]. There are not many studies that focus on employment needs of young people with NMDs during transition into adulthood. As reported by Lindsay et al. [85], transition plans from an occupational point of view are insufficient. Young people with NMDs experience severe disadvantages during transition to adulthood, especially in pursuing meaningful occupations, such as school, volunteering, employment, social and recreational activities. Thus, unemployment, social isolation and depression are widespread among this population. An important intervention in this area could be geared to increase self-esteem of young patients with NMDs [40].

Discussion

This review highlights how transition from pediatric to adult care in NMDs is a process not just encompassing physical aspects but also psychological and social ones. It thus required a multidisciplinary approach (Fig. 1). The literature on transitional care is still fragmented and vague, although the increasing importance of psychosocial factors [10,86,87].

However, it is indisputable that correct physical programming is essential for a transition with positive outcomes. Periodic and continuous checks regarding the medical condition, pharmacological and genetics and a preparation of the patient regarding his own diagnosis and prognosis are very important aspects. Collaboration between professionals is an essential condition for a successful transition. A gap in transition planning emerges for most adolescents, both with and without mental, behavioural and/or developmental disorders [88].

The findings of this review, even if not systematic, can be grouped into three macro-areas of interest: health

and physical needs, young patients' and caregivers' psychological needs, and social aspects.

Regarding psychological care, young patients are more likely to show internalizing and externalizing problems (such as anxiety, depression, aggression) during this phase, as seen in some studies [59]. Moreover, anxiety seems to mediate the relationship of negative coping and transition readiness in youths [89]. Furthermore, social involvement – in general – and social closeness with peers – in particular – are related to the patients' well-being [82,83].

Another aspect that should not be overlooked is caregiver distress [71]. Parental or caregiver stress increases in the transition period mainly due to problems with social interaction [90].

Clearly, children and adolescents have different needs and demands (medical, psychological and social) which need be reconciled. For an optimal transition, physical care, emotions, social involvement, education, sexuality, family implications, job possibilities, and advocacy need to be addressed. Improving transition from adolescent to adult health care may be considered a real goal to achieve good care outcomes for individuals with chronic conditions [91]. This shows once again how an optimal transition process involves the collaboration of several professionals [45] and active participation of patients and caregivers.

Conclusions

This work has some limitations. Indeed, this is a non-systematic review of the literature. For this reason, it lacks an explicit intent to maximize scope or analyse data collected, and therefore there could be some bias [34], but our main purpose was to stress that transition should not only be planned taking into consideration physical aspects but also psychological and social aspects, namely implementing a multidisciplinary model of intervention [92]. We found that few or no studies explored the transition process from pediatric to adult care in neuromuscular diseases and attempted to identify a general pattern of transition applicable to all NMDs. Studies in the literature provide fragmented findings due to the different manifestations of NMDs and do not delve into topics such as sexual activity, family planning or the social impact of neuromuscular diseases [10] or do the psychosocial aspects [8,93]. Most studies do not report longitudinal or outcome data on successful transition in patients with NMDs. It might be useful to start drafting unique general guidelines for the transition process from pediatric to adult care that can take into account physical, psychological and social aspects and that can be applied to all patients with NMDs. Rather than drawing up general guidelines, the greatest

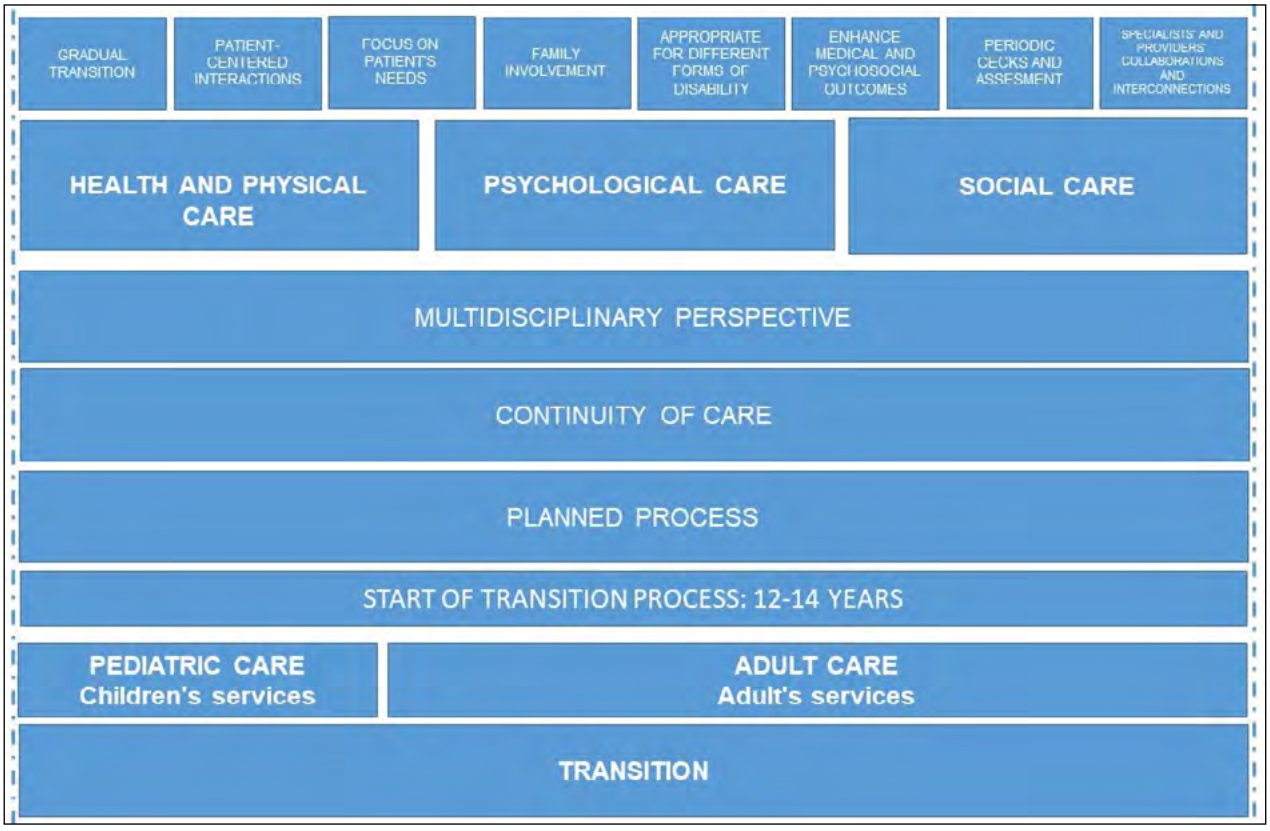

Figure 1. Successful factors for transition from pediatric to adult care in a multidisciplinary perspective.

difficulties could arise on a practical level. For example, it may be difficult to interconnect and coordinate a large number of individuals or to afford the costs, given that patients would have to be followed up by multiple specialists or specialists may not be adequately trained in the field of transition [6].

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Conflict of interest statement

The authors declare no conflict of interest.

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Author's contributions

GA, AT: study conceptualization and design. CF, MCO, IG, IF and MDR: literature search and data extraction. GA and AT: original draft of the manuscript. AT and GA: critical revision of the manuscript. Finally, all the authors approved the final version of the manuscript.

Ethical consideration

The research was conducted ethically, with all study procedures being performed in accordance with the requirements of the World Medical Association's Declaration of Helsinki.

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Supplementary Table I. Articles containing the selected key words in the title and/or in the abstract. Main purpose and consistency with the topic of this review.

Authors	Year	Title	Journal	Aim	Main topic and coherence with this review
Fleischer et al.	2022 [6]	Essen transition model for neuromuscular diseases	Neurological Research and Practice	Structuring a transition process with an interdisciplinary collaboration to improve patients' quality of life	Presentation of a structured transition process for some neuromuscular pathologies established at Essen University Medical Center. Psychosocial aspects are not addressed in detail
Cheng et al.	2020 [38]	Transition of patients with neuromuscular disease and chronic ventilator-dependent respiratory failure from paediatric to adult pulmonary care	Paediatric Respiratory Reviews	Identifying difficulties and needs in transition for patients with neuromuscular diseases and chronic respiratory failure.	In-depth analysis of pshysical and psychological aspects, but mainly focus on breathing difficulties
Willis	2020 [25]	Transition from pediatric to adult care for young adults with chronic respiratory disease	Respiratory Care	Increasing clinician awareness of health care transitions of young adults with chronic respiratory disease	Detailed definition of transition and description of a successful transition. Focuses are on chronic respiratory problems that could be also caused by NMDs

Supplementary Table I. Continues.

Authors	Year	Title	Journal	Aim	Main topic and coherence with this review
Menon et al.	2022 [45]	Clinical profile and multidisciplinary needs of patients with neuromuscular disorders transitioning from paediatric to adult care	Neuromuscular disorders	Description of the spectrum of neuromuscular diseases evaluated through a pediatric to adult neuromuscular transition program and various issues requiring specific services. The study suggests the need of multidisciplinary clinical care	Focus on the physical and psychosocial aspects (the latter are not very detailed). Particular attention on issues of different services. Importance of a multidisciplinary clinical perspective
Paguinto et al.	2020 [95]	Multidisciplinary perspectives and practices of wheelchair prescription for children with neuromuscular conditions	Disability Rehabilitation. Assistive Technology	Understanding healthcare professionals' clinical perspectives and practices when recommending wheelchair equipment for the first time for pediatric neuromuscular disorders	Transition as the passage from deambulation to wheelchair in children with progressive NMDs
Burns et al.	2014 [96]	The cerebral palsy transition clinic: administrative chore, clinical responsibility, or opportunity for audit and clinical research?	Journal of Chlidren's Orthopaedics	Clear communication needs with children with cerebral palsy in transition to adult services	Definition of transition and focus mainly on physical aspects and little on the psychological ones. Focus only on cerebral palsy
Ambrosini et al.	2019 [94]	"Be an ambassador for change that you would like to see": a call to action to all stakeholders for co-creation in healthcare and medical research to improve quality of life of people with a neuromuscular disease	Orphanet Journal of Rare Diseases	Investigating the position of neuromuscular patients in a European foundation of patient organisations with respect to health care and medical conditions to identify and address gaps and bottlenecks	Focus on "shared decision making" (SDM) and on patient involvement. Particular attention on patient involvement and on psychosocial aspects
Wasilewska et al.	2020 [42]	Transition from childhood to adulthood in patients with Duchenne Muscular Dystrophy	Medicina	Overview of healthcare needs related to the transition from pediatric care to adult care in patients with DMD	Focus on physical and psychosocial aspects of transition, but only on DMD patients

Supplementary Table I. Continues.

Authors	Year	Title	Journal	Aim	Main topic and coherence with this review
Sonneveld et al.	2013 [97]	Gaps in transitional care: what are the perceptions of adolescents, parents and providers?	Child: Care, Health and Development	Exploring perspectives in adolescents with chronic conditions, their parents and providers on transitional care. Exploring the extent to which such perspectives are disease-specific	Other pathologies in addition to neuromuscular ones are taken as example (juvenile rheumatoid arthritis, diabetes Type I). Main focus on participants' perspective and their experiences with transitional care
Baldanzi et al.	2016 [98]	Hard ways towards adulthood: the transition phase in young people with myotonic dystrophy	Acta Myologica	Identifying areas of unmet needs and targeted health objectives that ensure support to myotonic dystrophy type 1 (DM1) population	Main focus on psychosocial aspects during transition process. However, it focuses on DM1
Paguinto et al.	2020 [99]	"It's not just the wheelchair, it's everything else": Australian parents' perspectives of wheelchair prescription for children with neuromuscular disorders	Disability and Rehabilitation	Investigating parents' perception or their experiences of their child's transition to wheelchair equipment	Transition seen as the passage to wheelchair for children with neuromuscular disorders. Focus on parents' perspectives and experiences
Tripodoro & De Vito	2015 [48]	What does end stage in neuromuscular diseases mean? Key approach-based transitions	Current Opinion in Supportive and Palliative Care	Providing a definition of end stage in neuromuscular diseases, highlighting the implications for patients, family and healthcare team	Transition seen as the move to supportive and palliative care. Focus on physical and psychosocial issues
Lu et al.	2019 [100]	Transition to adult care in sleep medicine	Paediatric Respiratory Reviews	Considering the common barriers to transition and reflect on the specific barriers relating to patients managed by the sleep medicine team	Main focus on barriers in transition process, but particular attention on sleep medicine

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Torin1 restores proliferation rate in Charcot-Marie-Tooth disease type 2A cells harbouring MFN2 (mitofusin 2) mutation

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Objective. Mitofusin 2 (MFN2) is a mitochondrial outer membrane protein that serves primarily as a mitochondrial fusion protein but has additional functions including the tethering of mitochondrial-endoplasmic reticulum membranes, movement of mitochondria along axons, and control of the quality of mitochondria. Intriguingly, MFN2 has been referred to play a role in regulating cell proliferation in several cell types such that it acts as a tumour suppressor role in some forms of cancer. Previously, we found that fibroblasts derived from a Charcot-Marie-Tooth disease type 2A (CMT2A) patient with a mutation in the GTPase domain of MFN2 exhibit increased proliferation and decreased autophagy. Methods. Primary fibroblasts from a young patient affected by CMT2A harbouring c.650G > T/p.Cys217Phe mutation in the *MFN2* gene were evaluated versus a healthy control to measure the proliferation rate by growth curves analysis and to assess the phosphorylation of protein kinase B (AKT) at Ser473 in response to different doses of torin1, a selective catalytic ATP-competitive mammalian target of rapamycin complex (mTOR) inhibitor, by immunoblot analysis. Results. Herein, we demonstrated that the mammalian target of rapamycin complex 2 (mTORC2) is highly activated in the CMT2A^{MFN2} fibroblasts to promote cell growth via the AKT(Ser473) phosphorylation-mediated signalling. We report that torin1 restores CMT2A^{MFN2} fibroblasts' growth rate in a dose-dependent manner by decreasing AKT(Ser473) phosphorylation. Conclusions. Overall, our study provides evidence for mTORC2, as a novel molecular target that lies upstream of AKT to restore the cell proliferation rate in CMT2A fibroblasts.

Key words: Charcot-Marie-Tooth type 2A2, mitofusin2, AKT, cell proliferation, mTORC2

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Introduction

Charcot-Marie-Tooth disease type 2A (CMT2A) (OMIM 609260), is an autosomal dominant inherited sensorimotor neuropathy affecting peripheral nerve axons, that has causative mutations in the mitofusin 2 (*MFN2*) gene located in chromosome 1 (chr1:11.998.820). This gene encodes for mitofusin 2 (*MFN2*) protein which is related to dynamin family GTPases. MFN2 protein has pleiotropic cellular roles, which include participation in mitochondrial fusion, mitochondria–endoplasmic reticulum

tethering, mitochondrial trafficking along axons, and mitochondrial quality control [1]. MFN2 is also involved in the regulation of cell survival and for this reason, it has been of interest in the cancer field [2]. Cellular proliferation is closely dependent on the dynamics of mitochondria as it has been shown that high levels of mitochondrial fission are associated with active proliferation and the maintaining of mitochondrial hyper-fused morphology can regulate the cell transition from G1 to the S phase [3,4]. To date, several studies in CMT2A harbouring a mono-allelic mutation in MFN2 with autosomal dominant inheritance have not been conclusive on the molecular mechanisms causing cellular alterations. Efforts have been mainly focused on respiratory chain capacity, oxidative phosphorylation [5,6], mitochondrial membrane potential [6] or mitochondrial DNA (mtDNA) content [5,7], reporting extremely variable results, whereas most of the studies about the role of MFN2 in autophagy and proliferation have been performed in tumour cells. In a previous study, we analyzed both the mitochondrial and cellular phenotypes in CMT2A^{MFN2} fibroblasts harbouring a monoallelic MFN2$^{650G>T/C217F}$ mutation in the GTPase domain [8,9], which has been classified as "likely pathogenic" from the ACMG [10]. We found that CMT2A^{MFN2} fibroblasts presented an increase in the so-called intermediate-fragmented mitochondria; an inefficient capacity in recovering mitochondria morphology upon removal of a stressful insult; the depolarization of the mitochondrial membrane, and impaired respiration due to a significant reduction of respiratory complexes' activities. Hence, we asked whether the presence of damaged mitochondria in CMT2A^{MFN2} cells would promote their clearance through the stimulation of autophagy/mitophagy. We observed a decrease in autophagosome formation leading to a reduction of the autophagy process initiation and consistent acceleration of cell division. Interestingly, we found that amongst the highest differentially expressed genes in CMT2A^{MFN2} fibroblasts, those controlling cell proliferation, extracellular matrix organization, and the phosphoinositide 3-kinase (PI3K)/AKT/mTOR signalling pathway were mostly represented [8,9]. Based on this evidence and on the findings that mTORC2/AKT signalling pathway is highly elevated in MFN2 knocked-out cancer cells [11], we decided to verify whether mTORC2 activation was involved in the regulation of CMT2A^{MFN2} fibroblasts proliferation. In the present paper, we studied the AKT(Ser473) phosphorylation which is the target of the mTORC2 kinase activity [12-14] and consistently found that mTORC2-AKT signalling is activated in CMT2A^{MFN2} cells. We showed that treatment with torin1, a pharmacological and competitive inhibitor of mTOR, resulted in attenuation of CMT2A^{MFN2} fibroblasts proliferation rate, suggesting that this pathway is an important actor in CMT2A pathogenesis.

Materials and methods

Cell culture and reagents

Primary fibroblasts from a young patient affected by CMT2A^{MFN2} (c.650G>T/p.Cys217Phe) and a healthy control (individual with no histological or biochemical signs of mitochondrial disease), were obtained as reported in [8] after informed consent. Cells were grown in high-glucose Dulbecco's modified Eagle's medium (DMEM; EuroClone, ECB7501LX10) supplemented with 10% (v/v) fetal bovine serum (FBS; EuroClone, ECS5000L), 1% (v/v) L-glutamine (E EuroClone, ECB3000D), 1% (v/v) penicillin/streptomycin (EuroClone, ECB3001D), 50µg/ml of uridine (Sigma-Aldrich, U3003), in a humidified incubator at 37°*C and 5% CO2 avoiding confluence at any time.* All experiments were performed on cells with similar passage numbers, ranging from 5 to 8, to avoid any artefact due to senescence. For the experiments, growing cells were plated on sterile plastic dishes or flasks and allowed to adhere for at least 24 h before use. Torin1 (MedChemExpress, USA) was used at 0.1, 0.25 and 0.5 µM for 72 h, and DMSO as a vehicle.

Growth curves

CMT2A^{MFN2} fibroblasts and control cells were seeded in 24-well plates and grown for 3 days in presence of torin1 at 0.1, 0.25 and 0.5 µM and DMSO as vehicle-only treatment conditions. Cells were harvested by trypsinization and counted by hemocytometer every 24 h from day 1 to day 3. Cells were examined with Zeiss Primovert (Zeiss, Germany). A total of three individual experiments were performed.

Immunoblot analysis

For each treatment, fibroblasts grown on plates were collected at the confluence and homogenized in RIPA buffer (ThermoFisher Scientific, 89900) supplemented with proteases (Cell Signaling, 5871) and phosphatase (Cell Signaling, 5870S) inhibitors. The cells were sonicated on ice and centrifuged for 10 min at 16,000×g at 4°C and the protein concentrations were determined by Bradford assay (Bio-Rad, 500-0006). Thirty *µg* of cell proteins were lysed and denatured in Laemmli Buffer 2X (Bio-Rad, 1610737) separated by SDS-PAGE using homemade 10% separating gel and then transferred onto PVDF membranes using a Trans-Blot transfer apparatus (Bio-Rad, California, USA). The blocking agents used were 5% nonfat dry milk before overnight incubation with anti-phospho AKT (Ser473) and anti-GAPDH and Everyblot (Bio-Rad, 12010020) before overnight incubation with anti-total AKT antibodies.

Western blots were performed using primary anti-

bodies at the dilution of 1:1000 for anti-phospho AKT (Ser473) (Cell Signaling Technology D95), 1:2000 for anti-total AKT (Cell Signaling Technology, 40D4) and 1:15000 for anti-GAPDH (ProteinTech, 60004-1-Ig). Peroxidase Affinity Pure goat anti-mouse IgG and goat anti-rabbit IgG (Bio-Rad, 1706516 and 1706515, respectively) were added for 1 h at room temperature in the same buffer used for the primary antibodies. According to the manufacturer's instructions, reactive bands were detected using Clarity Western ECL Substrate (Bio-Rad, 1705061). Image acquisition was performed by the LI-COR C-Digit blot scanner and densitometric analysis was performed by the Image Studio Acquisition software (Licor, Lincoln, NE).

Statistical analysis

All statistical analyses were performed using PRISM® 7.04 in analytical software (GraphPad Software Inc, San Diego, CA) and Excel (Microsoft, Inc.). Results were expressed as average values ± SD of at least three independent determinations, each performed in triplicate, if not otherwise specified using CMT2A^{MFN2} versus sex and age-matched control fibroblasts. Statistical significance was calculated using Student's t parametric test set at: *$p < 0.05$; **$p < 0.01$; and ***$p < 0.001$; and ****$p < 0.0001$. A one-way analysis of variance (ANOVA) test was performed to examine the differences between more than two dependent groups. The Bonferroni correction was used for multiple comparisons.

Results

Torin-1 restores CMT2A^{MFN2} fibroblasts' growth rate by decreasing AKT(Ser473) phosphorylation in a dose-dependent way

We have already demonstrated that inhibition of AKT activity with miransertib restores cell proliferation and autophagy in CMT2A^{MFN2} fibroblasts' [8,9]. To further dissect the mTOR/AKT signalling pathway involvement, we used a selective catalytic ATP-competitive mTOR inhibitor, *i.e.,* torin1, to reverse the effect of mTOR activation and prove that it is involved in the increase of cell proliferation rate of CMT2A^{MFN2} fibroblasts. We evaluated the antiproliferative activity of torin1 at 0.1, 0.25 and 0.5 μM for 72 h. We showed that the treatment caused a decrease in CMT2A^{MFN2} fibroblast growth rates compared to vehicle-only (DMSO)-treated cells as well as for the control fibroblasts according to the different inhibitor doses (Fig. 1). Since cell proliferation is controlled by mTORC2 through AKT(Ser473) phosphorylation [12-14], we evaluated mTORC2 activity by measuring the level of AKT-phosphorylation at Ser473 in CMT2A^{MFN2} fibroblasts. We found a very significant increase of AKT(Ser473) phosphorylation in basal conditions of CMT2A^{MFN2} compared to control fibroblasts. The inhibition by torin1 reduced AKT(Ser473) levels more strikingly in the mutant rather than in control fibroblasts. In detail, when we compared the levels of AKT(Ser473) at 0.5 uM torin1, we found no signal in mutant compared to control fibroblasts, despite the level of AKT(Ser473) in untreated conditions being much higher in mutant than in control. Furthermore, torin1 treatment was able to significantly reduce the abundance of AKT(Ser473) in a dose-dependent manner in CMT2A^{MFN2} fibroblasts (Fig. 2). The decreased cell proliferation rate reflected the different levels of AKT phosphorylation at Ser473. Taken together, these results suggested that the mTORC2 pathway is more activated in CMT2A^{MFN2} than in healthy control fibroblasts and highlighted the dependence of cell proliferation on this signalling pathway.

Discussion

The molecular mechanism by which MFN2 mutations lead to the disease and, importantly, how this mechanism can be tackled to modify CMT2A2's natural history is intensely studied [1,5-7,15-17]. Recently, our laboratory has shown that human CMT fibroblasts harbouring heterozygous single nucleotide substitution c.650G > T in MFN2, featured increased cell proliferation and downregulation of the autophagy process initiation. The transcriptomic analysis helped us to deep into the molecular pathways responsible for the dysfunctions found in CMT2A^{MFN2} fibroblasts. Most of the differentially expressed genes were enriched in cell population proliferation, extracellular matrix organization, and PI3K/AKT/mTOR signalling pathway. PI3K/mTOR/AKT signalling pathway has been proven to serve an important role in regulating cell proliferation, differentiation, autophagy, and apoptosis [18-22].

Based on this evidence, we showed that AKT activation is crucial in the regulation of proliferation in CMT2A^{MFN2} fibroblasts. Previously, we proved that the selective pharmacological inhibition of AKT with miransertib allowed for the restoration of the autophagy and cell proliferation rate in CMT2A^{MFN2} cells [8,9]. In the present study, we deepened the molecular mechanism responsible for the increased cell proliferation in CMT2A^{MFN2} fibroblasts focusing on mTORC2. We considered that mTORC2 mainly controls cell proliferation through the regulation of the phosphorylation *status* of AKT at Ser473 [12-14]. To this aim, we investigated AKT phosphorylation in CMT2A^{MFN2} cells, using torin1, a selective catalytic ATP-competitive mTOR inhibitor. Our results provide evidence of a strong increase of mTORC2-dependent phosphorylation of AKT(Ser473) in mutant fibroblasts. Torin1 treatment

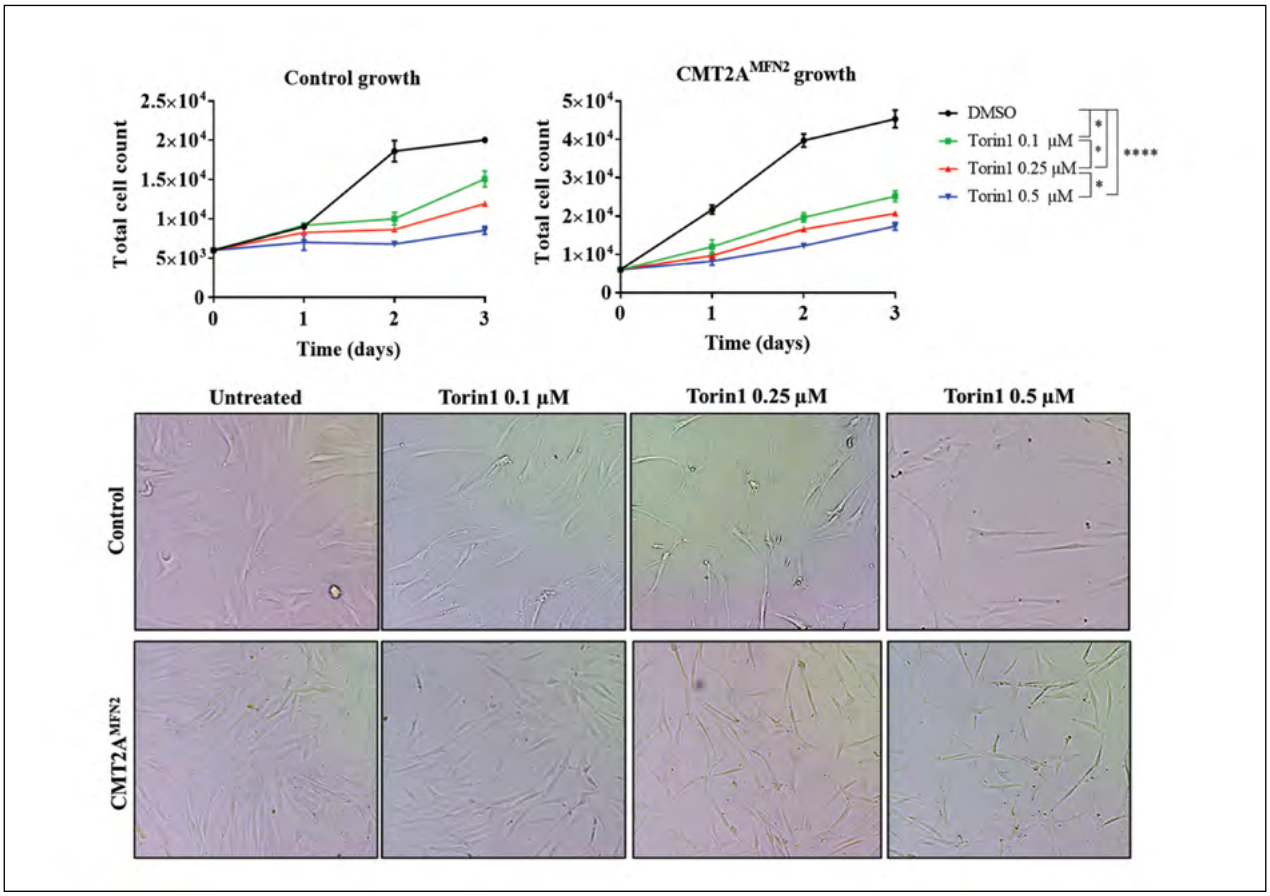

Figure 1. The cell growth rate of control and CMT2A^{MFN2} fibroblasts treated both with torin1 at 0.1, 0.25 and 0.5 µM and only vehicle (DMSO) for 72 h. Representative images of cells treated both with vehicle (DMSO) and torin1 at 0.1, 0.25 and 0.5 µM are shown. Data are presented as mean ± SD (n = 3). P-values refer to both control and CMT2A^{MFN2} fibroblasts. Student's t-test; $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. A one-way ANOVA test with Bonferroni's correction was performed for multiple comparisons.

showed anti-proliferative activity in CMT2A^{MFN2} cells by decreasing AKT(Ser473) phosphorylation in a dose-dependent manner. We derived that in agreement with the known anabolic effects of mTORC2/AKT pathway activation, the CMT2A^{MFN2} fibroblasts showed a remarkable increase in cell proliferation that can be reduced by the pharmacological targeting of mTORC2. This study reinforces our previous results confirming the involvement of the mTORC2/AKT pathway in CMT2A^{MFN2} disease. Acting on this pathway both miransertib and torin1 produce similar effects on cell proliferation. Herein, we showed that this pathway, extensively studied in cancer, can also be important in the pathogenesis of the neurodegenerative disease. PI3K/AKT/mTOR pathway is necessary to promote growth and proliferation over differentiation of adult stem cells, neural stem cells specifically [23]. It would be worth investigating the role of the PI3K/AKT/mTOR pathway in a cell system closely related to the disease, such as neuronal stem cells generated from CMT2A2 patients to understand if PI3K/AKT/mTOR signalling alterations could impact neural stem cell survival/differentiation. Overall, our results unveil mTORC2/AKT as novel potential targets that play a role in CMT2A2 pathophysiology.

Conclusions

In conclusion, our evidence showed that CMT2A^{MFN2} fibroblasts harbouring heterozygous single nucleotide substitution c.650G > T MFN2 showed increased proliferation because of mTORC2 activation. Considering that MFN2 is defined as a tumour suppressor, and based on our previous findings, we can hypothesize that MFN2 mutation may act as a dominant trait on cell proliferation, giving thus an unchecked trait on the cell division. Torin1 treatment can restore the cellular growth rates of

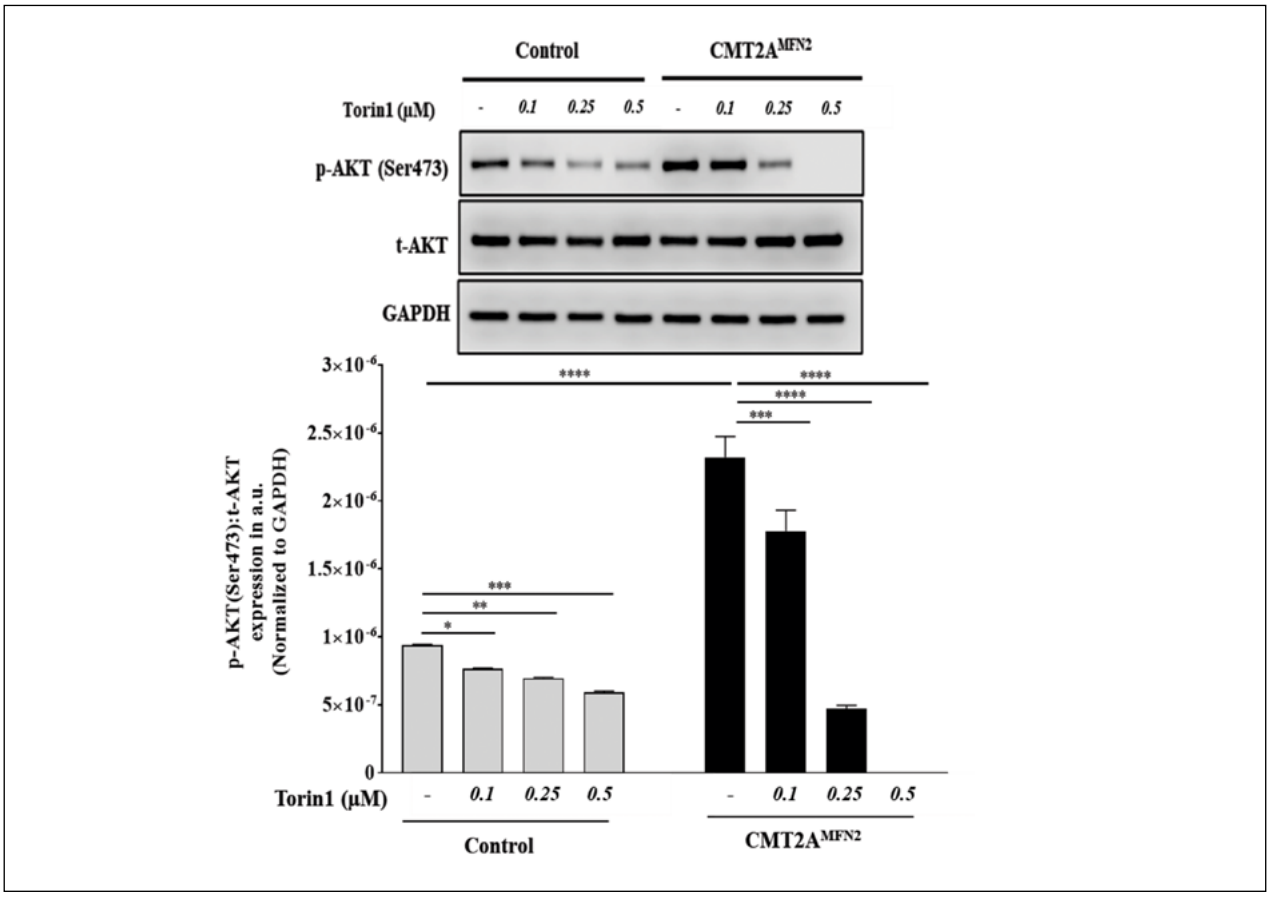

Figure 2. Representative western blot images of p-AKT(Ser473) and t-AKT in total cell lysates from CMT2A^{MFN2} and healthy control fibroblasts treated with torin1 at 0.1, 0.25 and 0.5 μM and vehicle-only (DMSO) for 72 h. Each signal was normalized to the GAPDH signal and densitometrical analysis of p-AKT(Ser473):t-AKT was performed. Data are presented as mean ± SD (n = 3). Student's t-test; $^{*}P < 0.05$; $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$. A one-way ANOVA test with Bonferroni's correction was performed for multiple comparisons.

CMT2A^{MFN2} fibroblasts in a dose dependent-manner acting on the AKT(Ser473) phosphorylation. Overall, these data established the dependence of cell proliferation on the mTORC2 pathway that thus represents a new potential actor in CMT2A2 pathophysiology.

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Conflict of interest statement

All authors have read and agreed to the published version of the manuscript. The Authors alone are responsible for the content and writing. No potential competing interest was reported by the authors.

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Author's contributions

PZ, VP: designed the research; FMS: provided the CMT2A^{MFN2} fibroblasts; PZ, AA, EAP: performed the research and analyzed the data; PZ, VP: wrote the manuscript.

Ethical consideration

As reported in ref. 8, the family's patient signed informed consent for research use of clinical data.

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SCIENTIFIC LETTER

The Performance of Upper Limb (PUL) module in limb-girdle muscular dystrophy

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[*]Equal contribution

Limb-girdle muscular dystrophy (LGMD) is a genetic muscle disorder causing weakness and wasting of the proximal limb musculature. When ambulation is lost, the attention must be shifted to the upper limb muscles' function. We studied the upper limb muscle strength and the corresponding function in 15 LGMDR1/LGMD2A and 13 LGMDR2/LGMD2B, through the Performance of Upper Limb scale and the MRC score of upper limbs. The proximal item K and the distal items N and R were lower in LGMD2B/R2. The mean MRC score of all the muscles involved linearly correlated (r2 = 0.922) for item K in LGMD2B/R2. The functional worsening paralleled the muscles weakness in LGMD2B/R2. By contrast, at proximal level the function of LGMD2A/R1 was preserved despite muscle weakness was present, presumably due to compensatory strategies. Sometimes the combination of parameters might be more informative than considering them separately. PUL scale and MRC might be interesting outcome measures in non-ambulant patients.

Key words: Performance of Upper Limb (PUL version 1.2) scale, limb-girdle muscular dystrophy, LGMD2A/R1, LGMD2B/R2, MRC score

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Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of genetic muscle disorders with variable age of onset, primarily causing weakness and wasting of the proximal limb (i.e., the hip/shoulder girdle) musculature. Based on inheritance, LGMD was initially divided into two main subgroups: autosomal dominant and autosomal recessive (LGMD1 and LGMD2) [1].

The two most common forms of LGMD2/R in Italy are LGMDR1/LGMD2A and LGMDR2/LGMD2B [2]. Calpainopathy or LGMDR1/LGMD2A is an autosomal recessive LGMD characterised by progressive, symmetric proximal muscle weakness contractures, scapular winging without cardiac manifestations and sparing of pulmonary function [3]. The onset of weakness begins in early childhood or as late as 20 years of age. Severity varies, worse with earlier onset and with null mutations at both alleles.

Dysferlinopathy is caused by mutations in the *DYSF* gene, which encodes the skeletal muscle protein dysferlin [3]. The most common clinical diagnoses associated with dysferlinopathy are limb girdle muscular dystro-

phy type 2B (LGMDR2/LGMD2B) and a distal posterior myopathy (Miyoshi myopathy 1 MM1)[2]. Onset typically occurs during young adulthood, and clinical presentation is inconsistent, with a wide range of ages of onset, patterns of muscle weakness, and severity. Disease progression is variable, with loss of ambulation occurring 5 to 35 years after the onset of muscle weakness, while a small number of patients remain only mildly affected for decades [3,4].

Due to the promising ongoing preclinical studies, there is a high need to obtain natural history data in order to reach trial readiness. Very few studies focused on the natural history of LGMD2A/R1 and 2B/R2 have been reported [5-7]. Most studies in LGMD focused their attention on different aspect of the diseases such as motor, cardiac and respiratory function [8] but the authors' attention was mainly focused on lower limb and loss of ambulation.

The need also for non-ambulant patients to access to clinical trial is essential in these days. In this case, the attention must be necessarily shifted and dedicated to upper limb muscles' function.

According to the pathology, upper limb residual abilities are clinically assessed with a variety of outcome measures. These include the Fugl-Meyer Motor Scale, the Action Research Arm Test (ARAT), the Barthel Index, the Brooke scale and the Motor Function Measure (MFM). However, these scales do not allow the identification of functional changes in short time-lapse.

The Performance of Upper Limb (PUL) scale was designed specifically to measure the upper limb motor performance of Duchenne muscular dystrophy (DMD) [9]. The spectrum of DMD severity ranges from weak ambulant male children to non-ambulant patients with limited residual finger movements. The PUL scale testes the proximal to distal progression of muscle weakness in DMD through three levels: high (shoulder domain), mid (elbow domain), and distal (wrist and finger domain). The PUL score (version 1.2) includes 22 items related to functional tasks that patients and clinicians identified as relevant. Nine items are dedicated to proximal (i.e., mid-level elbow) level. These comprise bringing hand(s) to mouth and to table from lap, moving weight on table, lifting light and heavy cans, stacking light and heavy cans, removing lid from container and tearing paper. Eight items are dedicated to distal (i.e., wrist and fingers) level. These comprise: tracing a path, push on the light, turning light, picking up coins, placing fingers on number diagram, lifting with finger pinch grip, lifting with 3 point grip and lifting with thumb (key) grip [9].

Reliability of PUL in non-ambulant DMD patient and in different muscular dystrophies such as LGMD and BMD has been shown [10].

For this reason, we evaluated the PUL score in 28 LGMD patients: 15 LGMD2A/R1 (8 females, 3 ambulant) and 13 LGMD2B/R2 (6 females, 3 ambulant). As expected, the disease onset was earlier in LGMD2A/R1 (median age: 10 years) compared to LGMD2B/R2 (median age: 20 years, $p < 0.001$); while median disease duration at time of evaluation was similar (respectively 24 and 29 years, $p = 0.106$). Consequently, LGMD2A/R1 patients were younger than LGMD2B/R2 patients were (median age: 33.4 *vs* 51.2 years, $p < 0.001$).

Table I reports all the items that were not significantly different between the two groups. Of note, all items related to the shoulder (from B to E) were zero for both dystrophies. The shoulder girdle was completely compromised as almost all patients were not able to perform shoulder abduction or flexion, neither to or above shoulder height. Figure 1 reports the items (namely, K, N and R) that significantly differed between the two groups of patients, being lower in LGMD2B/R2. More in detail, item K corresponds to a function involving proximal muscles (stacking light cans) whereas item N and R to functions depending on distal muscles (tearing paper and picking up coins, respectively).

In all these patients, the MRC score of upper limbs was also administrated to assess muscles strength. For items K, N and R, the mean MRC score of all the muscles involved in the required function was calculated. Trapezius, deltoids and biceps brachialis muscles were pooled for item K, being lower in LGMD2A/R1 (Fig. 1). Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles were pooled for item N. Wrist extensor, opponent of the thumb, interosseous and hand grip muscles were pooled for item R. Figure 2 shows the correlations between muscular strength (i.e.: mean MRC score) and the function (i.e.: item) for item K, N and R. The dystrophies showed two well distinct patterns for item K. While reduced muscular strength corresponded to reduced function in LGMD2B/R2 with a strong linear regression ($r2 = 0.922$), the function of LGMD2A/R1 was independent on the muscles strength (Figure 2, left panel). Although the upper limb girdle muscles in all but one LGMD2A/R1 patients were weaker (i.e.: MRC < 3), the function of stacking light cans was almost preserved presumably due to compensation mechanisms/strategies.

Similarly, all but two LGMD2A/R1 patients were able to fully tear paper even in presence of weakness (MRC < 3) of the muscles specifically involved in the function. On the other hand, only LGMD2B/R2 patients whose upper limb muscles were relatively strong (i.e.: MRC > 3) fully achieved the task of item N; while LGMD2B/R2 patients with moderate to severe muscular weakness showed impaired function (Figure 2, middle panel).

Finally, the distal muscles of the hand were preserved in the majority of patients, independently of the type of dystrophy so that they were able to pick up coins, therefore accomplishing the task required by item R (Figure 2, right panel).

Table I. Items and times of the PUL that were not significantly different between the LGMD2A/R1 and LGMD2B/R2 patients. Data are expressed as median, 25th percentile (25th p) and 75th percentile (75th p).

			LGMD2A/R1			LGMD2B/R2		
		Description	*Median*	*25th p*	*75th p*	*Median*	*25th p*	*75th p*
High level shoulder dimension	Item A	Entry item	3.0	2.0	3.0	2.5	1.8	3.0
	Item B	Shoulder abduction to shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item C	Shoulder abduction above shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item D	Shoulder flexion to shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
	Item E	Shoulder flexion above shoulder height	0.0	0.0	0.0	0.0	0.0	0.0
Mid level elbow dimension	Item F	Hand(s) to mouth	2.0	1.5	3.0	1.5	0.0	2.3
	Item G	Hand(s) to table from lap	3.0	3.0	3.0	3.0	2.0	3.0
	Item H	Move weight on table	2.0	1.0	4.0	1.5	1.0	4.3
	Item I	Lifting light cans	5.0	0.0	5.0	5.0	0.0	5.0
	Time I		5.2	3.4	7.0	5.7	5.0	6.0
	Item J	Lifting heavy cans	3.0	0.0	5.0	3.0	0.0	5.0
	Time J		2.4	0.0	4.3	5.2	3.1	6.5
	Time K	Stacking light cans	8.6	6.4	11.3	8.8	5.3	9.8
	Item L	Stacking heavy cans	4.0	3.5	4.0	3.0	0.0	4.0
	Time L		9.8	6.1	12.8	7.4	5.2	9.9
	Item M	Remove lid from container	1.0	1.0	1.0	1.0	0.8	1.0
Distal wrist and hand dimension	Item O	Tracing path	4.0	4.0	4.0	4.0	3.0	4.0
	Item P	Push on the light	3.0	3.0	3.0	3.0	2.8	3.0
	Item Q	Turning light	2.0	2.0	3.0	2.0	2.0	3.0
	Item S	Placing finger on number diagram	3.0	3.0	3.0	3.0	3.0	3.0
	Item T	Lifting with finger pinch grip	2.0	2.0	2.0	2.0	2.0	2.0
	Item U	Lifting with 3 point grip	2.0	2.0	2.0	2.0	2.0	2.0
	Item V	Lifting with Thumb (key) grip	3.0	3.0	3.0	3.0	3.0	3.0
	TOT		50.5	41.0	54.5	50.0	28.5	53.0

Several authors suggest that understanding the impact of muscular weakness on daily activity and function is essential for the quality of life of these patients as well as for prompting clinical (pharmacological and/or rehabilitative) interventions. Taken together, the results of this pilot study showed that the performance of the upper limb of the two considered forms of LGMD2/R differed for only three items (one proximal and two distal), being all lower in LGMD2B/R2. In addition, different patterns were found in the function-strength relationship. The functional worsening paralleled the muscles weakness in LGMD2B/R2. At proximal level (item K), the correlation between function and muscular strength was very strong, while it was apparently weaker at distal level. However, the two distal functions were preserved in the majority of LGMD2B/R2 corresponding also to acceptable muscle strength. A part for a couple of outliers, the other patients showing muscular weakness had also lower functions. Only for item R, this function-strength correspondence was found in LGMD2A/R1 whose function and muscle strength almost reached their maximum scores. By contrast, at proximal level the function was preserved despite muscle weakness was present and similar to LGMD2B/R1. Muscular weakness, therefore, did not correspond to impaired function, presumably due to compensatory strategies commonly adopted in this dystrophy.

Our protocol allowed to study the upper limb more in detail. When we previously studied the clinical evolution of LGMDR we concluded that in both dystrophies, the impairment of the upper limbs seemed to be equally distributed

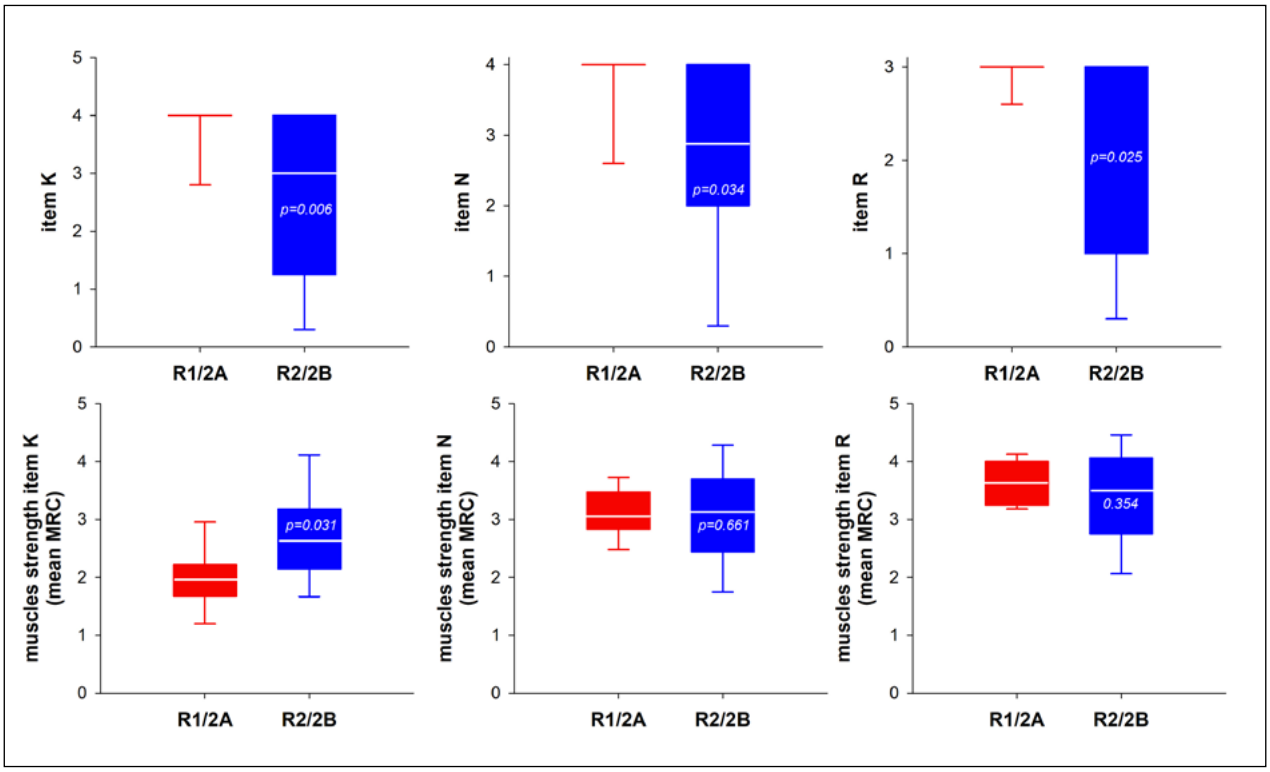

Figure 1. Box-and-whisker plot representing the median (white line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the item K (top left, i.e.: stacking light cans), N (top middle, i.e.: Tearing paper) and R (top right, i.e.: Picking up coins) of the PUL score measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. Box-and-whisker plot representing the median (white line within the box), the interquartile range (length of the box), the 90th and the 10th percentiles (whiskers above and below the box) of the mean MRC score of all the muscles involved in item K (bottom left, i.e.: Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles), N (bottom middle, i.e.: Biceps brachialis, triceps brachialis, wrist extensor and flexor, opponent of the thumb and hand grip muscles) and R (bottom right, i.e.: Wrist extensor, opponent of the thumb, interosseous and hand prehension muscles) of the PUL score measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. The p-values are also reported in white.

between the shoulder girdles and the arms, with a relatively spared wrist. This conclusion came from the evaluation of only the muscular strength through MRC scale [6]. Future studies should investigate if the supposed different compensatory strategies explained the different pattern found by considering also the function in addition to the muscular strength. Indeed, LGMD2A/R1 were weaker but with almost preserved item K function. These results are relevant because they showed how the informational content of clinical test might change if its results were considered alone or in combination with others, as for the function-strength discrepancy found in LGMD2A/R1 for item K. Physicians should be aware that sometimes the combination of parameters might be more informative than considering them separately. More studies need to be undertaken either to collect natural history either to identify reliable outcome measures in non-ambulant patients with slowly progressive muscular dystrophies [6], with upper limb playing the major role.

Acknowledgements

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Conflict of interest statement

The authors declare no conflict of interest.

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Author's contributions

DE, DAMG: study conception and design; DE, DFM, CR: data collection; ALM, DE, DAMG: analysis

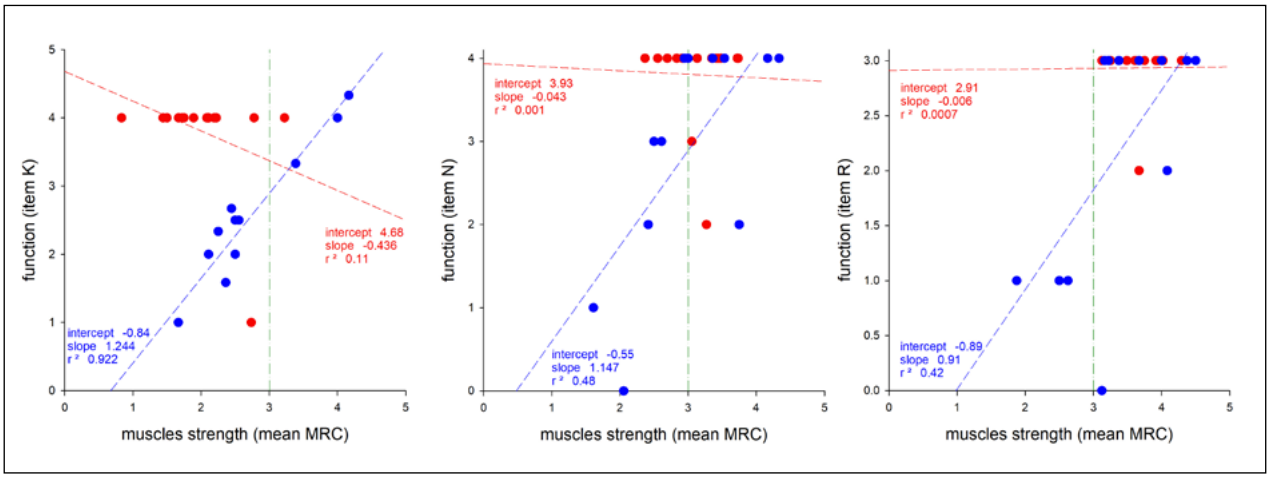

Figure 2. Scatter plot of the mean muscles MRC score (*x-axis*) and the corresponding function (*y-axis*) measured on LGMD2A/R1 (R1/2A, red) and LGMD2B/R2 (R2/2B, blue) patients. The mean muscles MRC score for item K (left, i.e.: stacking light cans) was computed by calculating the average of the MRC score of the trapezius, the deltoids and the biceps brachialis muscles. The mean muscles MRC score for item N (middle, i.e.: Tearing paper), was computed by calculating the average of the MRC score of the biceps brachialis, the triceps brachialis, the wrist extensor and flexor, the opponent of the thumb and the hand grip muscles. The mean muscles MRC score for item R (right, i.e.: Picking up coins) was computed by calculating the average of the MRC score of the wrist extensor, the opponent pollicis, the interosseous and the hand prehension muscles were pooled. The intercept and the slope of the linear regression lines (short-dashed lines) as well as the coefficient of determination (r^2) are also shown. The vertical dash-dotted green lines indicate the threshold when muscle contracts and moves with no resistance.

and interpretation of results; ALM, DAMG: draft manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

Ethical consideration

All the evaluations were performed following standard care guidelines for LGMD and all the retrospective data were anonymised. All patients or parents/legal tutors signed informed consent to anonymous data analysis, approved by the local ethics committee according to the declaration of Helsinki.

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NEWS FROM AROUND THE WORLD

AIM

The activities carried out by the Association in the fourth trimester 2022 mainly focused on the organization of the national congress.

The 22nd National Congress of the Italian Association of Myology took place in Matera (South Italy) from 19 to 22 October 2022, and was a success in terms of attendance, with an overall participation of around 300 people in all four days of the congress.

The scientific program was very active and intensive, with four lectures – two of them held by guests of international renown, such as Prof. Jerry Mendell from the Nationwide Children's and the Ohio State University (USA) and Prof. Jordi Diaz-Manera from Newcastle (UK) – 5 workshops, 2 special sessions and 5 company symposia. There were also numerous (42) oral communications, while a great success and participation was the discussion of posters (77).

The Congress concluded the works with the assignment of n. 5 prizes to young researchers (Fig. 1). In particular, the following awads have been assigned:

1. The "Giovanni Nigro" prize for the best oral communication on muscular dystrophies, kindly offered by the Neapolitan Association Gaetano Torre Centre for Muscular Dystrophy, was awarded to dr. Giulio Gadaleta (University of Turin) for the contribution "Adults with Duchenne Muscular Dystrophy (DMD): old and new challenges in a long-living cohort";
2. The "Parent Project Italia" prize for the best oral communication was awarded to dr. Daniele Sabbatini (University of Padua), for the contribution "Genome-Wide Association Study for identification and characterization of genetic modifiers of Duchenne muscular dystrophy"
3. The "AIM" prize for the best oral communication was awarded to Dr. Carmen Campanale, (University of Bari) for the contribution "Functional and pharmacological characterization of a Nav1.4 sodium and a ClC-1 chloride channel mutations segregating with myotonia in an Italian kindred".
4. The "AIM" prize for the best poster was awarded to Dr. Rossella Cima (IRCCS Medea, Bosisio Parini) for the contribution "Twenty years of natural history of Myotonic dystrophy type 1";
5. The "AltroDomani" prize for the best poster was awarded to Andrea Barp (Nemo Clinical Center in Milan) for the contribution: "Body composition and myokines in a cohort of patients with Becker muscular dystrophy".

The following event "Breathless and moveless - Neuromuscular disorders in intensive care", held in Udine on 22 October 2023, was also sponsored.

The 23rd Congress of AIM will be held in Padua from 5 to 8 June 2023.

Figure 1. The winners of the prizes assigned during the 22nd Congress of the Italian Association of Myology.

MSM

Due to pandemics, the 14th Meeting of the Mediterranean Society of Myology (MSM) is moved to the 2023. Proposals to organize and host the event are welcome.

WMS

The 27th International Annual Congress of the World Muscle Society took place on 11th-15th October 2022, in Halifax, Nova Scotia, Canada, in a hybrid manner. The congress venue was the Halifax Convention Centre at 1650 Argyle Street, in the heart of this Atlantic seaport. Figure 2 shows a synthesis of the Congress activities.

During the Congress there was the election of the new Scientific Board. Six members stepped down: Carsten Bönnemann, Nathalie Goemans, Carmen Navarro, Anders Oldfors, Haluk Topaloğlu, Peter Van den Bergh and six new members joined: Lindsay Alfano, Alan Beggs, Jordi Diaz-Manera, Teresinha Evangelista, Gina Ravenscroft, Benedikt Schoser. This was the first in-person congress since the three current Executive Officers were elected, and they all put themselves forward to stand again and were accepted: Volker Straub (President), Laurent Servais (Secretary), Gisèle Bonne (Treasurer).

The future WMS Congresses will be in Charleston, South Carolina (2023); Prague, Czech Republic (2024); Vienna, Austria (2025) and Hiroshima, Japan (2026).

For further information visit the Society website *https://worldmusclesociety.org*

Figure 2. The 27th WMS congress in pills.

FORTHCOMING MEETINGS

2022

December 7-8

The 4th International Conference on Rare Diseases. Vienna, Austria. Information: website: *www.bioevents.net*

2023

January 9-11

12th World Gene Convention. Sapporo, Japan. Information: website: *https://www.bitcongress.com/WGC2023*

March 24-26

ESC Acute CardioVascular Care 2023. Marseille, France. Information: website: *https://www.escardio.org/Congresses-Events/Acute-Cardiovascular-Care*

April 20-22

Sorrento breathing. Update and new trends on respiratory medicine. 13rd Edition. Information: website: *www.Centercongressi.com*

April 16-18

EHRA Congress - European Society of Cardiology. Barcelona, Spain. Information: website: *https://www.escardio.org/Congresses-Events/EHRA-Congress*

April 22-28

75th AAN Annual Meeting. Boston, MA. USA. Information: website: *https://www.aan.com*

May 9-12

4th International Meeting on Laminopathies, Madrid, Spain. Information: website: *https://www.laminopathy2023.com*

May 10-12

EACVI 2023. Barcelona, Spain. Information: website: *https://www.escardio.org/Congresses-Events/EACVI-Congress*

May 20-23

Heart Failure 2023 and World Congress on Acute Heart Failure. Prague, Czech Republic. Information: website: *https://www.escardio.org/Congresses-&-Events/Heart-Failure*

May 23-24

Digital Health World Congress 2013.London, UK. Information: website: *https://digitalhealthcareworldcongress.com*

May 25-26

International Conference on Neuroscience and Neurology, Tokyo, Japan. Information: website: *https://www.neuralscience.scientexconference.com*

June 5-8

23rd National Congress of the Italian Association of Myology. Padua, Italy. Information: website: *www.miologia.it*

July 1-4

9th EAN Congress. Budapest, Hungary. Information: website: *https://www.ean.org*

August 25-28

ESC Congress 2023. Amsterdam, The Netherlands. Information: website: *https://www.escardio.org/*

September 13-14

International Conference and Expo on Heart and Cardio Care. Rome, Italy. Information: website: *https://hilarisconferences.com/heart/contact*

October 3-7

28th Congress of World Muscle Society. Charleston, USA. Information: website: *https://worldmusclesociety.org*

October 9-11

International Congress on Genetics and Genomics. Dubai, UAE. Information: website: *https://signatureconferences.com/genetics-genomics23/*

October 15-19

VCN2023. XXVII World Congress of Neurology. Montreal, Canada. Information: website: *https://wcn-neurology.com*

October 19-21

4th ENMD Congress. Munich, Germany. Information: website: *www.enmd-neuromuscular.eu; info@fclassevents.com*

2024

April 13-19

76th AAN Annual Meeting. Denver, CO. USA. Information: website: *https://www.aan.com*

June 29 - July 2

10th EAN Congress. Helsinki, Finland. Information: website: *https://www.ean.org*

October 8-12

29th Congress of World Muscle Society. Prague, Czech Republic. Information: website: *https://worldmusclesociety.org*

2025

April 5-11

77th AAN Annual Meeting. San Diego, CA. USA. Information: website: *https://www.aan.com*

October 7-11

30th Congress of World Muscle Society. Vienna, Austria. Information: website: *https://worldmusclesociety.org*

VOLUME XLI - LIST OF REFEREES CONSULTED IN 2022

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For application or renewal to MSM

MEDITERRANEAN SOCIETY OF MYOLOGY* (MSM)

APPLICATION/RENEWAL FORM

Application/Renewal for **1yr** ☐ **2 yrs** ☐

Prof. Luisa Politano, Cardiomiologia e Genetica Medica, Primo Policlinico, piazza Miraglia, 80138 Napoli, Italy
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Fax or Mail to the above address. Type or print.

Name _____ Degree(s) _____
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Institution _____

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* Amount payable: 1 year Euro 100
2 years Euro 180

❑ I enclose copy of the bank transfer to:

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Account holder: MSM-Mediterranean Society of Myology
IBAN code: IT36 F030 6909 6061 0000 0160 879
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INSTRUCTIONS FOR AUTHORS

Acta Myologica publishes articles related to research in and the practice of primary myopathies, cardiomyopathies and neuromyopathies, including observational studies, clinical trials, epidemiology, health services and outcomes studies, case report, and advances in applied (translational) and basic research.

Manuscripts are examined by the editorial staff and usually evaluated by expert reviewers assigned by the editors. Both clinical and basic articles will also be subject to statistical review, when appropriate. Provisional or final acceptance is based on originality, scientific content, and topical balance of the journal. Decisions are communicated by email, generally within eight weeks. All rebuttals must be submitted in writing to the editorial office.

Starting from 2020, a publication fee of 200 Euros is required. The Corresponding Author must fill in the appropriate form and send it with the corrected proofs. 50% off is offered for members of Associazione Italiana di Miologia (AIM) and/or Mediterranean Society of Myology (MSM) in good standing with dues. A copy of the payment receipt for the current year is mandatory to prove the membership).

On-line submission

Manuscript submission must be effected on line: www.actamyologica.it according to the following categories:

Original articles (maximum 5000 words, 8 figures or tables). A structured abstract of no more than 250 words should be included.

Reviews, Editorials (maximum 4000 words for Reviews and 1600 words for Editorials). These are usually commissioned by the Editors. Before spontaneously writing an Editorial or Review, it is advisable to contact the Editor to make sure that an article on the same or similar topic is not already in preparation.

Case Reports, Scientific Letters (maximum 1500 words, 10 references, 3 figures or tables, maximum 5 authors). A summary of 150 words may be included.

Letters to the Editor (maximum 700 words, 5 references). Letters commenting upon papers published in the journal during the previous year or concerning news in the myologic, cardio-myologic or neuro-myologic field, will be welcome. All Authors must sign the letter.

Rapid Reports (maximum 400 words, 5 references, 2 figures or tables). A letter should be included explaining why the author considers the paper justifies rapid processing.

Lectura. Invited formal discourse as a method of instruction. The structure will be suggested by the Editor.

Congress Proceedings either in the form of Selected Abstracts or Proceedings will be taken into consideration.

Information concerning new books, congresses and symposia, will be published if conforming to the policy of the Journal.

The manuscripts should be arranged as follows: 1) Title, authors, address institution, address for correspondence; 2) Repeat title, abstract, key words; 3) Text; 4) References; 5) Legends; 6) Figures or tables. Pages should be numbered (title page as page 1).

Title page. The AA are invited to check it represents the content of the paper and is not misleading. A short running title is also suggested.

Key words. Supply up to six key words. Wherever possible, use terms from Index Medicus – Medical Subject Headings.

Text. Only international SI units and symbols must be used in the text. Tables and figures should be cited in numerical order as first mentioned in the text. Patients must be identified by numbers not initials.

Illustrations. Figures should be sent in .jpeg or .tiff format. Legends should be typed double-spaced and numbered with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, each should be explained clearly in the legend. For photomicrographs, the internal scale markers should be defined and the methods of staining should be given.

If the figure has been previously published a credit line should be included and permission in writing to reproduce should be supplied. Color photographs can be accepted for publication, the cost to be covered by the authors.

Patients in photographs are not to be recognisable

Tables. Tables should be self-explanatory, double spaced on separate sheets with the table number and title above the table and explanatory notes below. Arabic numbers should be used for tables and correspond with the order in which the table is first mentioned in the text.

References. Indicate all Authors, from 1 to 3. If their number is greater than 3, indicate only the first 3, followed by “et al.” . Arabic numbers in the text must be superscript. References in the list must be numbered as they appear in the text, with the reference number superscript. **DOI name must be included with each reference** (when available). If not available, indicate the PMID number.

Examples of the correct format for citation of references:

Journal articles: Shapiro AMJ, Lakey JRT, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230-238. doi.org/10.14639/0392-100X-1583

Books and other monographs: Dubowitz V. Muscle disorders in childhood. London: WB Saunders Company Ltd; 1978.

Please check each item of the following checklist before mailing:

- Three-six index terms, short title for running head (no more than 40 letter spaces) on the title page.
  Name(s) of the author(s) in full, name(s) of institution(s) in the original language, address for correspondence with email address on the second page.
- Summary (maximum 250 words).
- References, tables and figures cited consecutively as they appear in the text.
- Figures submitted actual size for publication (i.e., 1 column wide or 2 columns wide).
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- References prepared according to instructions.
- English style.
- Patients in photographs not recognisable.