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Title

The European Neuromuscular Centre Consensus Statement on Anaesthesia in Patients with Neuromuscular Disorders

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ene.15526

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Total word count (including title page, references, and structured abstract): 9483

Running title: Anaesthesia and Neuromuscular Disorders

Key words: Anaesthesia, malignant hyperthermia, myopathy, neuromuscular disorders, peri-operative care.

ACKNOWLEDGEMENTS

We are thankful to the ENMC who financially supported the 259th ENMC workshop. Several authors are members of the Radboud-NMD, NL-NMD, EURO-NMD and the TREAT-NMD consortium.

We would like to dedicate this consensus statement to the late Professor Ron Litman, he participated and contributed to the first workshop session.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The ENMC did not influence the content of this consensus statement.

ABSTRACT (word count 250; maximum 250)

Background Patients with neuromuscular conditions are at increased risk of suffering peri-operative complications related to anaesthesia. There is currently little specific anaesthetic guidance concerning these patients. Here we present the European Neuromuscular Centre (ENMC) consensus statement on anaesthesia in patients with neuromuscular disorders as formulated during the 259th ENMC workshop on Anaesthesia in neuromuscular disorders.

Methods International experts in the field of (paediatric) anaesthesia, neurology and genetics were invited to participate in the ENMC workshop. A literature search was conducted in PubMed and EMBASE whose main findings were disseminated to the participants and presented during the workshop. Depending on specific expertise, participants presented the existing evidence and their expert opinion concerning anaesthetic management in six specific groups of myopathies and neuromuscular junction disorders.

The consensus statement was prepared according to the Appraisal of Guidelines for REsearch & Evaluation (AGREE II) reporting checklist. The level of evidence has been adapted according to the Scottish Intercollegiate Guidelines Network (SIGN) grading system. The final consensus statement was subjected to a modified Delphi process.

Results A set of general recommendations valid for the anaesthetic management of patients with neuromuscular disorders in general have been formulated. Specific recommendations were formulated for 1) neuromuscular junction disorders; 2) muscle channelopathies (non-dystrophic myotonia and periodic paralysis); 3) myotonic dystrophy (type 1 and 2); 4) muscular dystrophies; 5) congenital myopathies and congenital dystrophies and 6) mitochondrial and metabolic myopathies.

Conclusion This ENMC consensus statement summarizes the most important considerations for planning and performing anaesthesia in patients with neuromuscular disorders.

Key words: Anaesthesia, malignant hyperthermia, myopathy, neuromuscular disorders, peri-operative care.

INTRODUCTION

Patients with neuromuscular disorders (NMDs) are at increased risk of peri-operative complications related to anaesthesia. The reasons for this include associated cardiorespiratory morbidity; altered pharmacodynamics of anaesthetics and neuromuscular blocking agents (NMBAs); impaired temperature and glucose regulation; and specific risks associated with certain underlying genetic defects, or a combination of the above [1-3].

Whilst in recent years comprehensive standards of care have been formulated for the more common NMDs such as Duchenne Muscular Dystrophy (DMD) [4] and Spinal Muscular Atrophy (SMA) [5] there is lack of consensus guidance focusing on the anaesthetic management of NMDs throughout the range of neuromuscular conditions. Neurologists are often asked to share the specific considerations regarding their neuromuscular patients requiring surgery, anaesthesia or procedural sedation. Furthermore, neurologists who provide follow-up for patients with NMDs are well-placed to alert them to any perioperative risks specifically associated with their NMD, and the particular precautions to be taken in close liaison with anaesthesiologists [1].

We therefore present the European Neuromuscular Centre (ENMC) consensus statement on anaesthesia in patients with NMDs as discussed and formulated during the 259th ENMC Workshop on Anaesthesia in Neuromuscular Disorders [6]. This consensus statement provides a comprehensive and accessible overview with the aim to guide neurologists and anaesthesiologists, and to improve perioperative safety, optimize risk assessment and appropriate management of these patients.

METHODS

Our approach to developing this consensus statement was performed according to the Appraisal of Guidelines for REsearch & Evaluation (AGREE II) reporting checklist [7].

ENMC workshop

For the 259th ENMC workshop on Anaesthesia in NMDs, 30 international experts in the field of (paediatric) anaesthesia, neurology and genetics were selected by the workshop organisers (NV, MS, SR, HJ) based on their particular expertise in anaesthesia and/or NMDs and geographic balance. The ENMC research board approved the participants list. The virtual workshop consisted of three parts:

I. Anaesthetic management of various NMDs (December 11th, 2020);
II. New developments in the field of MH and increasing awareness (May 28th, 2021);
III. Genetic counselling in patients with MH, rhabdomyolysis and related congenital myopathies (May 29th, 2021).

The comprehensive workshop report has been published separately [6] but did not allow for the inclusion of the full anaesthesia considerations included in this paper.

In preparation for the ENMC workshop, the organisers conducted a literature search covering the period January 1st, 2000 to July 14th, 2021 in PubMed and EMBASE using the methodological framework for scoping reviews [8]. The main findings of this literature search were disseminated to the participants and presented during the first part of the workshop. Furthermore, six couples of workshop participants were invited to present the existing evidence and their expert opinion for anaesthetic management in specific groups of NMDs (see below). These participants provided a written summary of their recommendations, which were merged to a preliminary version of this consensus statement. The presenters were subsequently invited to participate in a virtual meeting to discuss the preliminary consensus statement. After the initial evaluation, a revised version was distributed as a basis for discussion during the second part of the ENMC workshop. Subsequently, the preliminary consensus statement document was modified according to the discussion at the second workshop session and distributed by email. Consensus regarding the consensus statement content was reached after further communication by email. Finally, the consensus statement content was subjected to a modified Delphi process [9]. The whole process description is summarized in **Figure 1.**

Modified Delphi process

The consensus statement drafted following the ENMC workshop and subsequent meetings was distributed among its co-authors (n = 22). They were asked to indicate their agreement for each recommendation on a 9-point scale (score 1: absolutely disagree, score 9: absolutely agree). Given the variable and specific expertise of the workshop participants, for some of them the full content of this consensus statement was not completely within their area of expertise. The participants were asked to withhold from voting if a specific

recommendation was not within their area of expertise. The level of agreement for each recommendation is presented as the median score and the percentage of participants who scored ≥7. Consensus was defined as a median score of ≥7 and at least 70% of the respondents scoring the recommendation ≥7.

Focus and approach

This consensus statement entails general recommendations applicable to all patients with NMDs who need anaesthesia or procedural sedation and group-specific recommendations for:

- Neuromuscular junction disorders;
- Muscle channelopathies (non-dystrophic myotonia and periodic paralysis);
- Myotonic dystrophy (type 1 and 2);
- Muscular dystrophies;
- Congenital myopathies and dystrophies;
- Mitochondrial and metabolic myopathies.

Suggested relevant topics were risks, myopathy-related treatment, preoperative diagnosis and management, specific recommendation for anaesthesia including non-anaesthetic drugs used in the peri-operative phase and specific recommendations for postoperative care.
We restricted detailed clinical information concerning the six main groups of NMDs to what was essential for our purpose. For complementary disease-specific anaesthesia considerations we refer to the following databases:

- OrphanAnesthesia (https://www.orphananesthesia.eu/en/);
- Syndromes and rare diseases in paediatric anesthesia (http://tinyurl.com/PED-RARE).

As we consider the ASA physical status classification [10] too unspecific for this particular patient population, we devised a practical risk assessment tool with a scoring matrix based on the "NARCO-SS-risk assessment tool" [11] and the matrix model developed by *Schieren et al.* [2].

Level of evidence

The level of evidence for each recommendation has been adapted from the Scottish Intercollegiate Guidelines Network grading system [12] and is indicated in each paragraph:

- Level 1+ high quality meta-analyses, systematic reviews of randomized controlled trials (RCTs) or RCTs with very low risk of bias;
- Level 1- meta-analyses, systematic reviews or RCTs with high risk of bias;
- Level 2+ systematic reviews or case control or cohort studies with low risk of bias;
- Level 2- case control or cohort studies with high risk of bias, animal studies;
- Level 3 case reports, case series;
- Level 4 expert opinion.

RESULTS

Modified Delphi process

A total of 20 participants (90.9%) responded. During the modified Delphi process, consensus was reached for all recommendations.

LEVEL 1: General recommendations for patients with neuromuscular disorders

Surgery setting

Surgery and the associated need for sedation and/or anaesthesia pose a burden on the neuromuscular patient. They should only receive anaesthesia or sedation in settings with 24-hour high care facility [1-3].

Level of evidence: 4.

Median score modified Delphi process: 9. Respondents who scored ≥7; 18 of 19 (94.7%), one respondent abstained from voting.

Anaesthesia technique

Surgery or diagnostic procedures should be performed using regional anaesthesia if possible, preferably as a single technique or alternatively in combination with general anaesthesia [1-3].

Level of evidence: 4

Median score modified Delphi process: 8. Respondents who scored ≥7; 18 of 19 (94.7%), one respondent abstained from voting.

Preoperative assessment

A clear understanding of the confirmed or suspected neuromuscular diagnosis, degree of muscle weakness, current treatment and awareness of associated cardiorespiratory manifestations are paramount for the preoperative assessment. Cardiomyopathy or cardiac conduction defects can be part of certain NMDs [13-17]. Due to respiratory muscle weakness and spinal deformities there is an increased risk of restrictive lung disease [16, 18-20]. Furthermore, chronic hypoxaemia and pulmonary hypertension may lead to cor pulmonale, which must be considered during the preoperative examination [13]. This information can be partly obtained from the history or physical examination, but ancillary assessments may be necessary.

A careful preoperative examination, multisystem evaluation and clear communication among anaesthesiologists, surgeons, cardiologists, pneumologists and neurologists are crucial. During the preoperative assessment, specific attention should be paid to craniofacial abnormalities indicating a difficult airway [21]. Depending on the procedure, additional preoperative investigations may include ECG, chest X-ray, echocardiography, Holter examination, lung function tests (in the sitting and supine position), polysomnography and

blood tests including arterial blood gases, haemoglobin, electrolytes, lactate, creatine kinase (CK), liver and kidney function tests [1-3, 13-20, 22].
Some neuromuscular patients are treated with anticholinesterase inhibitors, anti-arrhythmic drugs, antisense oligonucleotides, steroids or other immunosuppressive agents [4, 23]. This needs to be recorded and evaluated during the preoperative assessment.

Level of evidence: 2+
Median score modified Delphi process: 9. Respondents who scored ≥7; 19 of 19 (100%), one respondent abstained from voting.

Premedication

Patients with NMDs have an increased sensitivity to sedatives and anaesthetics [1-3]. Premedication with benzodiazepines may result in central respiratory depression, airway obstruction and/or worsening of muscle weakness. Premedication should therefore be avoided, and if absolutely required only be used in reduced doses with concurrent pulse oximetry (SpO_2) and respiratory rate monitoring [1-3].

Level of evidence: 4
Median score modified Delphi process: 9. Respondents who scored ≥7; 19 of 19 (100%), one respondent abstained from voting.

Preoperative fasting

Patients with NMDs should be scheduled for surgery as the first case of the day since prolonged fasting may cause hypoglycaemia, in particular in patients with reduced muscle mass [24-26].

Level of evidence 2+
Median score modified Delphi process: 8. Respondents who scored ≥7; 14 of 16 (87.5%), four respondents abstained from voting.

Some NMDs are associated with gastro-intestinal dysmotility and dysphagia and the patient may not have an empty stomach [27]. Gastric ultrasound imaging could be used to evaluate the volume of gastric content before anaesthesia and adapt the induction technique accordingly [28].

Level of evidence 2+
Median score modified Delphi process: 8. Respondents who scored ≥7; 12 of 16 (75%), four respondents abstained from voting.

Body temperature management

Anaesthesia causes drop in body temperature due to vasodilation and blunting of thermoregulatory reflexes. This effect is more pronounced in neuromuscular patients because of their reduced muscle mass. Moreover, hypothermia further increases sensitivity to sedatives, anaesthetics and non-depolarising NMBAs [29]. Preoperative warming reduces the fall in core temperature following induction of anaesthesia in the general population [30] and will be even more beneficial in patients with NMDs.

Level of evidence: 4
Median score modified Delphi process: 9. Respondents who scored ≥7; 19 of 19 (100%), one respondent abstained from voting.

On the other hand, increased muscle activity (cramps, myotonia) or excessive external heating can result in hyperthermia with increased muscle tone, cramps and rhabdomyolysis. Therefore, continuous temperature monitoring is recommended.

Level of evidence: 4
Median score modified Delphi process: 9. Respondents who scored ≥7; 18 of 18 (100%), two respondents abstained from voting.

General anaesthesia

Short-acting opioids, sedatives and hypnotics are preferred to minimize respiratory depression on emergence from anaesthesia [1-3].

Level of evidence: 4
Median score modified Delphi process: 9. Respondents who scored ≥7; 18 of 18 (100%), two respondents abstained from voting.

Neuromuscular blocking agents

Based on their mechanisms of action, NMBAs can be divided into depolarising NMBAs and non-depolarising NMBAs [1]. Patients with an NMD are at greatest risk for succinylcholine-induced hyperkalaemia [31-34]. Hence, succinylcholine should not be used in patients with a known or suspected NMD.

Level of evidence: 2-
Median score modified Delphi process: 9. Respondents who scored ≥7; 19 of 19 (100%), one respondent abstained from voting.

Most neuromuscular patients have an increased sensitivity to non-depolarising NMBAs because of the reduced muscle mass and strength. A lower initial dose may be sufficient to achieve adequate muscle relaxation. Duration of action is often prolonged and effects of residual relaxation are more severe than in normal patients [35-38]. The effect of NMBAs

should be measured by quantitative neuromuscular monitoring to prevent residual neuromuscular blockade following emergence from anaesthesia and extubation.

Level of evidence: 2+
Median score modified Delphi process: 9. Respondents who scored ≥7; 18 of 18 (100%), two respondents abstained from voting.

When a non-depolarising NMBA is used, extubation and emergence from anaesthesia should be guided by a Train-Of-Four (TOF) ratio of 1.0. Any residual and potentially clinically relevant muscle relaxation at the end of the intervention should preferably be reversed with sugammadex as a specific pharmacological antagonist of rocuronium and vecuronium [39-41]. Due to the effectiveness of sugammadex, the latter two non-depolarising NMBAs should be given preference. When there is residual neuromuscular blockade after use of other NMBAs or sugammadex is unavailable, extubation and emergence from anaesthesia should be postponed until baseline muscular strength has recovered spontaneously. In this scenario, postoperative sedation and ventilatory support is necessary.

Level of evidence: 2-
Median score modified Delphi process: 9. Respondents who scored ≥7; 14 of 15 (93.3%), five respondents abstained from voting.

Reversal of muscle relaxation using cholinesterase inhibitors is contra-indicated because of side-effects in myotonic dystrophies [42, 43] and some congenital myasthenic syndromes. Cholinesterase inhibitors (*e.g.* neostigmine) are undesirable in other neuromuscular patients because of the unpredictable pharmacodynamics and the increased sensitivity to NMBAs.

Level of evidence: 2-
Median score modified Delphi process: 8. Respondents who scored ≥7; 12 of 16 (75%), four respondents abstained from voting.

Volatile anaesthetics

Volatile anaesthetics are only strictly contraindicated in patients with NMDs with variants in the *RYR1* gene because of the possibility of MH-susceptibility [44-50], unless the specific variant has been classified as benign for MH according to the ClinGen Variant Curation Expert Panel recommendations for *RYR1* pathogenicity classifications in MH-susceptibility [51]. Patients with variants in the *CACNA1S* and/or *STAC3* genes should be referred to an MH investigation centre for advice on the risk of MH before exposure to volatile anaesthetics.

Level of evidence: 2+
Median score modified Delphi process: 8. Respondents who scored ≥7; 11 of 15 (73.3%), five respondents abstained from voting.

NMDs without these specific genetic backgrounds might be associated with other, rare adverse effects, such as anaesthesia-induced rhabdomyolysis (AIR) in DMD or Becker muscular dystrophy (BMD) patients [33, 34]. The prolonged effect of NMBAs when used in combination with volatile anaesthetics also has to be taken into account [52].

Level of evidence: 2+
Median score modified Delphi process: 9. Respondents who scored ≥7; 18 of 18 (100%), two respondents abstained from voting.

Hence anaesthesiologists are advised against the prolonged use of volatile anaesthetics in patients with NMDs. Although often recommended as an alternative, total intravenous anaesthesia (TIVA, most frequently based on a propofol, short-acting benzodiazepines or dexmedetomidine-based technique in combination with short-acting potent opioids) has other risks [53-56]. This is an important consideration as part of a comprehensive risk-benefit assessment between TIVA and volatile anaesthetic-based techniques.
Specific indications for use of volatile anaesthetics (which can be administered through a face mask) in patients with an NMD might include situations where awake intravenous access is not tolerated or may be difficult or impossible, e.g. in anxious children.

Level of evidence: 4
Median score modified Delphi process: 8. Respondents who scored ≥7; 16 of 17 (94.1%), three respondents abstained from voting.

Postoperative period

After general anaesthesia or sedation, up to 24 hours monitoring (including ECG, SpO_2, preferably CO_2 monitoring, as well as surveillance for signs of ongoing rhabdomyolysis) may be necessary [1, 2].

Level of evidence: 4
Median score modified Delphi process: 8. Respondents who scored ≥7; 16 of 18 (88.9%), two respondents abstained from voting.

Early mobilisation and feeding after surgery should be pursued. Respiratory physiotherapy can improve breathing and facilitate coughing.

Level of evidence: 4
Median score modified Delphi process: 8. Respondents who scored ≥7; 17 of 18 (94.4%), two respondents abstained from voting.

Medical alert cards, apps and warnings in electronic patient files

Many patient advocacy organizations provide medical alert cards to patients with NMDs. These cards improve patient safety, supporting individuals and their families in relaying information to emergency services and other medical professionals. Specific and personalized disease information, possible complications and their specific treatments should be recorded in such formats.

Neurologists and rehabilitation specialists who provide follow-up for patients with NMDs are in an excellent position to alert their patients regarding perioperative risks and the specific precautions to be taken. Through annual review at follow-up visits, medical professionals can contribute to the improved use of medical alert cards. Medical alerts should be clearly visible in electronic health records, and recommendations for essential peri-operative precautions should be included in correspondence with other healthcare providers.

Level of evidence: 4

Median score modified Delphi process: 9. Respondents who scored ≥7; 19 of 19 (100%), one respondent abstained from voting.

LEVEL 2: Group-specific recommendations

In addition to the general recommendations summarized above, this section gives disease-specific recommendations concerning the six groups of NMDs.

1. Neuromuscular junction disorders

Disorders of the neuromuscular junction may be caused by pathogenic antibodies, genetic defects [57], specific drugs and/or toxins that interfere with the normal signalling between the presynaptic nerve ending and the postsynaptic muscle membrane [58].

Acquired autoimmune disorders of the neuromuscular junction are the most common and include myasthenia gravis [58, 59] and Lambert-Eaton Myasthenic Syndrome (LEMS). LEMS is frequently associated with an underlying malignancy or another autoimmune process.

Congenital myasthenic syndromes are a phenotypically heterogeneous group of disorders due to a variety of genetic defects resulting in impaired neuromuscular transmission. Muscle weakness typically begins in early childhood, but presentation may be delayed until adolescence or adulthood. Facial muscles, including (extra)ocular and bulbar muscles, are the most consistently affected. Due to muscle weakness, affected infants may have feeding difficulties. Motor development may be delayed. The severity of the myasthenia varies greatly, ranging from an inability to walk to only minor weakness. Weakness may be exacerbated by fever or infection [57, 58]. Specific anaesthesia considerations for patients with neuromuscular junction disorders are summarized in **Table 1**.

2. Muscle channelopathies

Skeletal muscle channelopathies are rare clinically and genetically heterogeneous diseases. They are characterized by altered muscle fibre excitability caused by mutations affecting voltage gated ion channels such as chloride channel (ClC-1), sodium channel (NaV1.4), calcium channel (CaV1.1), or potassium channels (Kir2.1, Kir2.6, Kir3.4). The clinical manifestations vary from an inability to relax after voluntary contraction (myotonia) to transient attacks of generalized or focal flaccid muscle weakness (periodic paralysis). Fluctuation of symptoms are strongly affected by environmental triggers such as exercise, temperature changes, pain, emotional factors, fasting or alterations in serum potassium concentration [63]. The non-dystrophic myotonias include myotonia congenita (due to variants in *CLCN1*), paramyotonia congenita (due to variants in *SCN4A*), and sodium channel myotonia (*SCN4A*) [23]. Periodic paralyses include hyperkalaemic periodic paralysis (hyperPP) caused by variants in *SCN4A* and hypokalaemic periodic paralysis (hypoPP) caused by variants in *CACNA1S* , *SCN4A [23, 64]* or rarely *RYR1* [65], and Andersen-Tawil syndrome caused by variants in *KCNJ2* [66]. Andersen-Tawil syndrome is associated with ECG abnormalities (long Q-T interval and U-waves) and predisposition to life-threatening ventricular arrythmias [14].

Up to 31% of patients with muscle channelopathies report worsening of symptoms and a prolonged recovery time after general anaesthesia [67]. There are reports of myotonic crises in patients with myotonias and prolonged paralysis (hyperkalaemic triggered by

succinylcholine or other potassium-releasing agents in patients with *SCN4A* variants and hypokalaemic related to hypokalaemia and hyperglycaemia following anaesthesia) [67, 68].
Variants in *CACNA1S* and, very rarely, *RYR1* are associated with hypoPP and while none of these *RYR1* variants has been shown to predispose to MH, the risk is difficult to disprove [65, 67, 69]. A patient with known hypoPP who had a confirmed episode of MH [69] has subsequently been found to harbour a *CACNA1S* variant pathogenic for hypoPP but also a second variant in *CACNA1S* and two variants in *RYR1* [48]; (unpublished data, PH). Specific anaesthesia considerations for patients with muscle channelopathies are summarized in **Table 2**.

3. Myotonic dystrophy type 1 and 2

Myotonic dystrophy type 1 (DM1) is a frequent adult muscular dystrophy caused by DNA triplet repeat expansion in the *DMPK* gene. Larger expansions lead to the infantile or more severe, congenital form resembling a congenital muscular dystrophy, with often profound associated weakness, hypotonia, bulbar and respiratory involvement. A second form of myotonic dystrophy, type 2 (DM2), results from a different repeat expansion in the *CNBP* gene, showing more proximal weakness [71].
Both disorders have autosomal dominant inheritance and multisystem features, including a myotonic myopathy, cataract, cardiac conduction defects, central and obstructive sleep apnoea, and a range of endocrine abnormalities including diabetes mellitus [71]. Respiratory impairment is more common and more pronounced in DM1.
Much of the available literature does not differentiate the congenital form of DM1 from its other forms, despite the facts that CTG repeat analysis [72] as well as grading by presence of proximal weakness [72, 73] argue for a higher risk of complications in the congenital form. Furthermore, myotonia is usually absent in the early life of patients with this form. Specific anaesthesia considerations for patients with myotonic dystrophy type 1 and 2 are summarized in **Table 3**.

4. Muscular dystrophies

Several different skeletal muscle disorders, with very different degrees of severity and characterized by various pathophysiological mechanisms, are classified under the definition of muscular dystrophies. These disorders vary widely with regards to age of onset, degree of motor impairment, and associated cardiorespiratory involvement [80]. Classification is based on the underlying gene defect. This paragraph will focus on the most common forms, the dystrophinopathies, limb girdle muscular dystrophies (LGMDs), facioscapulohumeral muscular dystrophy (FSHD) and oculopharyngeal muscular dystrophy (OPMD).
Dystrophinopathy refers to DMD and BMD due to hemizygous X-linked variants in the *DMD* gene, encoding dystrophin. Ventilatory support and steroid treatments has improved survival in boys with DMD significantly and has prolonged ambulation, reduced the risk of developing scoliosis and improved cardiac health [80]. Severe cardiorespiratory involvement is common and needs thorough evaluation during the pre-operative assessment [13, 17]. Macroglossia and neck muscles contracture can cause problems for intubation. CNS

involvement manifesting as cognitive deficits, speech problems and psychiatric comorbidities such as anxiety and depression may complicate pre-operative counselling [81]. LGMDs are a genetically heterogeneous group of disorders characterized by predominantly proximal muscle weakness and onset after becoming able to walk [80]. Specific forms (e.g., sarcoglycanopathies and alpha-dystroglycanopathies) may be associated with cardiac involvement, usually dilated cardiomyopathy or rarely, arrhythmogenic heart disease which is frequent in *POPDC1*-related LGMDR 25 [15, 16]. Respiratory failure may be a feature of the most severe forms or of those with spinal deformities, such as the *COL6*-related LGMDs. Significant tongue enlargement, that can cause problems for intubation, is occasionally present in *FKRP*-related LGMD R9, DMD and sarcoglycanopathies [16, 21].

Facioscapulohumeral muscular dystrophy (FSHD) is caused by skeletal muscle misexpression of the *DUX4* retrogene and represents the third most common form of muscular dystrophy in adults after DMD and DM1. Phenotypes may be variable and not immediately apparent in presymptomatic carriers [80].

Oculopharyngeal muscular dystrophy (OPMD) is another late-onset mostly autosomal dominant disorder caused by a trinucleotide repeat expansion in the first exon of the polyadenylate-binding protein nuclear 1 gene (*PABPN1*). The main clinical issues are ptosis and dysphagia, although patients may later also develop proximal muscle weakness. Specific anaesthesia considerations for patients with muscular dystrophies are summarized in **Table 4**.

5. Congenital myopathies and congenital muscular dystrophies

Congenital myopathies and congenital muscular dystrophies are disorders with early-onset muscle weakness. Both groups give rise to proximal, axial and often facial weakness with slow progression, cardiorespiratory impairment as well as joint contractures and scoliosis. Despite some overlap anaesthetic implications are different.

Congenital muscular dystrophies

Congenital muscular dystrophies are classically defined as a group of disorders characterized by onset in the first six months of life and muscle biopsy evidence of a muscular dystrophy with histopathological features of de- and regeneration [85]. Depending on the underlying disease, cardiorespiratory involvement can be prominent, while some forms may have associated CNS involvement with epilepsy. The genes associated can be classified according to the cellular localization of the encoded protein into the following groups. Proteins of the plasma membrane–extracellular matrix interface such as collagen 6 (*COL6A 1,2,3*), merosin or laminin α2 (*LAMA2*), integrin α7 (ITGA7), proteins involved in O-glycosylation of the dystrophin-associated glycoprotein (DAG) (*POMT1, POMT2, POMGnT1, LARGE, FKTN, FKRP, ISPD*) and other intracellular proteins such as lamin A/C (*LMNA)*, an intermediate filament located at the inner nuclear membrane, and selenoprotein N (*SELENON*), a protein with redox and calcium level regulation function [80].

It should be noted that the clinical phenotype of congenital DM1 (see paragraph above) is more similar to this group of diseases than to the adult forms of myotonic dystrophy. Specific anaesthesia considerations for patients with congenital muscular dystrophies are summarized in **Table 5A**.

Congenital myopathies

Congenital myopathies are a heterogeneous group of early-onset inherited disorders. The different subtypes are traditionally based on the predominant histopathological finding; nemaline rods, cores, central nuclei, or fibre type disproportion. There is, however, overlap between these findings and there is an emerging trend to define the conditions according to which gene is involved. There are over 20 genes associated with congenital myopathies. The overall prevalence is estimated at 2-4/100 000. [86-88] with *RYR1*-related myopathies the most common, followed by those due to variants in *NEB* and *ACTA1. TTN*-related myopathies are increasingly diagnosed and represent an important subgroup. The genes causing congenital myopathies predominantly encode proteins implicated in skeletal muscle Ca^{2+} homeostasis, excitation–contraction coupling, myofilament assembly and interaction, and other mechanisms [88]. Specific anaesthesia considerations for patients with congenital myopathies are summarized in **Table 5B**.

6. Mitochondrial and metabolic myopathies

Mitochondrial myopathies

Mitochondrial myopathies are caused by variants in either nuclear or mitochondrial DNA leading to impairment of oxidative phosphorylation or fatty acid metabolism in mitochondria. The accumulation of Acyl-CoA might result in a secondary carnitine deficiency and impair the citrate cycle, gluconeogenesis, the urea cycle, fatty-acid oxidation, resulting in a deficit in energy production in the form of adenosine triphosphate, particularly in skeletal muscle [22, 89]. In addition, patients with a mitochondrial myopathy can also present with multisystemic symptoms. Anaesthetic preparation should therefore always be case-specific and include a multisystemic assessment. Circumstances causing metabolic disturbance should be avoided in all mitochondrial myopathies whenever possible [22, 25, 89, 90]. Specific anaesthesia considerations for patients with mitochondrial myopathies are summarized in **Table 6A**.

Metabolic myopathies

Metabolic myopathies present with either permanent (fixed) muscle symptoms or episodic abnormalities, such as exercise-intolerance, activity induced myalgia, muscle contractures and muscle damage that can progress to rhabdomyolysis. Metabolic myopathies can be classified further as muscle glycogen storage diseases (GSD) (or muscle glycogenosis) and lipid metabolism disorders [22, 91, 92].

Muscle GSD are a group of inherited disorders that cause glycogen to be improperly stored or utilized in the body. Symptoms and comorbidities are highly diverse, some GSDs only affect skeletal muscle, while others feature involvement of other organs (including the heart and liver). This needs special focus as patients can be severely affected multi-systemically [22, 91, 92]. For instance, patients with GSD type II may present as classic Pompe disease with cardiomegaly, juvenile oligo-symptomatic cases or late-onset cases with weakness and often severe respiratory involvement. Specific anaesthesia considerations for patients with GSDs are summarized in **Table 6B**.

Muscle lipid metabolism disorders can also manifest in organs other than skeletal muscle. Abnormalities in enzyme processing fats can result in accumulation of fatty acid and its derivatives including triglycerides, and sterol-containing metabolites such as cholesterol. This can be harmful to the heart and liver and may result in cardiomyopathy, arrythmias, hepatomegaly, hypoglycaemia and hyperammonaemia [92]. Specific anaesthesia considerations for patients with muscle lipid metabolism disorders are summarized in **Table 6C**.

LEVEL 3: Risk prediction matrix and safety of non-anaesthetic drugs used in the perioperative period

Risk prediction matrix

Table 7 illustrates a preoperative assessment matrix designed as a practical tool based on *Schieren et al.* [2] which can be used to make an inventory of the multisystem features in patients with NMDs. A grey box in the risk prediction matrix indicates that at least a subset of this group of NMDs is associated with this specific condition/complication or disease manifestation. A white box indicates that this NMD is not specifically associated with this specific condition/complication or disease manifestation.

After obtaining the relevant information, the peri-operative risk can be obtained using the modified NARCO-SS tool. [11]. In this risk assessment tool, a score of 0, 1 or 2 is given for each organ system and/or specific scenario in the NARCO-SS acronym. A score of 0 indicates no signs or symptoms, a score of 1 indicates mild to moderate and a score of 2 indicates moderate to severe symptoms in the specific organ system. For the surgical severity (or "SS" in the acronym) a score of 0 is given for non-invasive or superficial elective procedures. A score of 1 is allocated for minimally invasive, elective procedures of up to 60 minutes duration with anticipated moderate blood loss. A score of 2 is given for major surgery/interventions or any type of surgery in an emergency setting.

- **N**: **N**eurological signs & muscular impairment? [0 – 1 – 2]
- **A**: Difficult **A**irway? [0 – 1 – 2]
- **R**: Symptoms of **R**espiratory disease? [0 – 1 – 2]
- **C**: Symptoms of **C**ardiac disease? [0 – 1 – 2]
- **O**: **O**ther co-morbidity or metabolic concerns? [0 – 1 – 2]
- **SS**: **S**urgical **S**everity? [0 – 1 – 2]

Result risk assessment, based on modified NARCO-SS:

1. Low risk: total score 0-4 with no individual score > 1;
2. Moderate risk: total score 5-6 with no individual score > 1;
3. High risk: total score 7-9 or any individual score of 2;
4. Seriously reconsider the indication for surgery and anaesthesia when total score above 9.

Unsafe non-anaesthetic drugs

Anaesthetists are often asked by surgeons or other physicians to administer other drugs *e.g.* antibiotics or antiepileptics. However, several of these drugs are possibly harmful for patients with NMDs. The following drugs should only be used with caution:

- Neuromuscular junction disorders
    - Oxazolidinone antibiotics (myasthenic crisis) [59, 102]
    - Aminoglycoside antibiotics (myasthenic crisis) [59, 102]

- Beta blocking agents (myasthenic crisis) [102]
- Botulinum toxin (myasthenic crisis) [102]
- Fluoroquinolone antibiotics (myasthenic crisis) [59, 102]
- Intravenous magnesium (myasthenic crisis) [58, 102]
- Macrolide antibiotics (myasthenic crisis) [59, 102]

- Muscle channelopathies
  - Potassium releasing agents (hyperkalaemic periodic paralysis) [23, 63]
  - β-agonist (hypokalaemic periodic paralysis) [63]
  - Insulin (hypokalaemic periodic paralysis) [63]
- Mitochondrial myopathies
  - Aminoglycoside antibiotics (ototoxicity) [95, 103]
  - Linezolid antibiotics (lactic acidosis) [95]
  - Metformin (lactic acidosis) [95, 103]
  - Valproic acid (liver failure) [95, 103]

Open questions

Because of the low prevalence of most NMDs, there is a lack of prospective clinical studies with a high level of evidence on the anaesthetic management of patients with NMDs resulting in several urgent open questions [8]. Observational multicentre studies can be of great value to study the prevalence of perioperative complications in patients with NMDs and the association with certain anaesthetic agents. One of the open questions is the future role of remimazolam, a recently introduced short-acting benzodiazepine. In patients with NMDs, neither propofol or volatile anaesthetics are ideal and short-acting benzodiazepines might be useful in this respect.

Another open question is how to manage a patient suspected of a yet undefined myopathy presenting for a procedure requiring anaesthesia (e.g. surgery, muscle biopsy, MRI). If it is a diagnostic procedure, it is worth establishing if lower-risk diagnostic options, especially DNA testing, have been exhausted.

Some recommend that volatile anaesthetics are best avoided. However, there is no high-level evidence on this topic, and this remains a matter of debate. Anaesthesiologists should exercise their own professional expertise and judgement to assess the disease-inherent and circumstantial risks to determine the most appropriate anaesthetic technique.

The following considerations may be helpful:

- Infants with congenital myopathies, the group at risk for MH [45, 46, 49, 50], and X-linked muscular dystrophies due to variants in the dystrophin gene, the group at risk for AIR [33, 34] usually have delayed motor milestones but cognitive development is usually normal [19, 20, 49, 88].
- Infants with hypotonia due to a metabolic disease, the group at risk for propofol infusion syndrome [54-56], usually present with global developmental delay or other neurological signs e.g. epilepsy and spasticity [22, 91, 92].

- Although non-specific, an increased baseline CK level, possibly points to a congenital myopathy or dystrophy. Therefore, these patients might be prone to AIR or MH susceptibility, and TIVA might be the preferred option.
- Laboratory evidence of metabolic derangements (*e.g.* elevated basal lactates) favour a metabolic, in particular mitochondrial myopathy [22, 92]. Volatile anaesthesia might be the preferred option in such cases as there is an increased risk of propofol infusion syndrome [54, 55].
- Although the balance of risks may be judged to favour a TIVA-technique for a particular child, an intravenous induction in an infant can be very challenging or impossible even when using nitrous oxide for sedation and topical local anaesthesia. The use of a short inhalation induction is an option in this situation, subsequently changing to TIVA once the intravenous line has been secured.

Nitrous oxide, barbiturates, benzodiazepines, ketamine, opioids, rocuronium, vecuronium and local anaesthetics are not linked to MH, AIR, propofol infusion syndrome, or other adverse events specifically linked to certain NMDs [104]. However, one must realize that there are no risk-free anaesthetic agents since each agent has its own specific risks, especially in patients with several and severe comorbidities such as neuromuscular patients [105].

Conclusion

This consensus statement summarizes the most important recommendations concerning anaesthesia in patients with NMDs. Since there have been no RCTs and only few large retrospective studies on this topic, most evidence is based on small case series and expert opinion, highlighting the need for future research. Prospective, observational studies using common databases would be of great value and may provide answers to several unresolved questions. However, carefully curated expert opinion-based recommendations can still be of value for health care professionals in the field of anaesthesia, NMDs and genetics. Given the low level of evidence, we expect an update of this consensus statement will be necessary in ten years or earlier in case of new highly relevant evidence outdates the content of this consensus statement.

LEGEND TO FIGURES AND TABLES:

Figure 1: A summary of the process description to developing this consensus statement document.
ENMC = European Neuromuscular Centre

Table 1: Specific anaesthesia recommendations for neuromuscular junction disorders
For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.
SIGN = Scottish Intercollegiate Guidelines Network

Table 2: Specific anaesthesia recommendations for muscle channelopathies
For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.
SIGN = Scottish Intercollegiate Guidelines Network

Table 3: Specific anaesthesia recommendations for myotonic dystrophy type 1 and 2
For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.
SIGN = Scottish Intercollegiate Guidelines Network

Table 4: Specific anaesthesia recommendations for muscular dystrophies
For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.
SIGN = Scottish Intercollegiate Guidelines Network

Table 5: Specific anaesthesia recommendations for congenital muscular dystrophies (5A) and congenital myopathies (5B)
For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.
SIGN = Scottish Intercollegiate Guidelines Network

Table 6: Specific anaesthesia recommendations for mitochondrial myopathies (6A), metabolic myopathies (6B) and lipid metabolism disorders (6C).

For each recommendation the level of evidence according to the SIGN criteria and the level of agreement is given by the median voting results and the percentage of respondents with a voting result ≥ 7.

SIGN = Scottish Intercollegiate Guidelines Network

Table 7: A risk prediction matrix to assess the multi-system features of patients with neuromuscular disorders.

A grey box in the risk prediction matrix indicates that at least a subset of this group of neuromuscular disorders is associated with this specific condition/complication or disease manifestation. A white box indicates that this neuromuscular disorder is not specifically associated with this specific condition/complication or disease manifestation.

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Table 1: Specific anaesthesia recommendations for neuromuscular junction disorders				
Specific considerations for Myasthenia gravis	**SIGN**	**Median score modified Delphi process**	**Respondents who scored ≥7**	**Abstained from voting (*n*)**
• Elective surgery should preferably be performed when the condition is stable with the patient requiring low doses of immunomodulatory medication and preferably as first case of the day when the weakness is least pronounced [59].	4	9	19/19 (100%)	1
• Consider postoperative complications: - *Myasthenic crisis*: severe respiratory muscle weakness that requires intubation or causes delayed extubation after surgery, linked to cholinergic deficit. Urgent therapy is needed with intravenous pyridostigmine, plasma exchange, immunoglobulins and/or supportive care [59]. - *Cholinergic crisis*: identified by the mnemonic "SLUDGE": Salivation, Lacrimation, Urination, Defecation, Gastrointestinal distress, and Emesis. Antimuscarinic (atropine) drugs must be given [59].	4	9	18/19 (94.7%)	1
Preoperative recommendations				
• An intravenous hydrocortisone stress regimen should be considered in patients who are or were recently (< 1 year) on a course of corticosteroids (prednisolone ≥ 5mg/day for > 1 month) [60].	4	8	15/17 (88.2%)	3
• Anticholinesterase agents should be continued until prior to surgery but stopped during anaesthesia.	4	9	17/19 (89.5%)	1
• Any immunosuppressive therapy other than steroids can be withheld on the day of surgery.	4	8	16/17 (94.1%)	3
• Inform the patient about the increased risk for perioperative complications, mainly postoperative pulmonary complications, myasthenic crisis and postoperative residual neuromuscular blockade [59].	4	9	19/19 (100%)	1
Intraoperative recommendations				
• TIVA and volatile anaesthetics have both been used effectively and safely and should be adapted to the case and surgery in question [59, 61, 62].	2-	9	15/15 (100%)	5
• Use of sugammadex rather than neostigmine is associated with a lesser risk of myasthenic crisis after thymectomy in adult myasthenia gravis patients [41].	2-	8.5	14/14 (100%)	6
Postoperative recommendations				
• Restart oral medication as soon as possible [59].	4	9	19/19 (100%)	1
• If intravenous administration of anticholinesterase agents is required, the dose should be adjusted: - Dose of oral pyridostigmine: intravenous pyridostigmine = 30:1 [59]; - Dose of oral pyridostigmine: intravenous neostigmine = 60:0.5 [58]. However, caution is needed since there are large inter-individual differences in bioavailability.	4	9	16/16 (100%)	4
• Pyridostigmine can also be administered by continuous infusion when the dose is adjusted accordingly. Following dose conversion as outlined above, the infusion can be terminated, and oral anticholinergics restarted at any point.	4	9	13/13 (100%)	7

Table 2: Specific anaesthesia recommendations for muscle channelopathies

Preoperative recommendations	**SIGN**	**Median score modified Delphi process**	**Respondents who scored ≥7**	**Abstained from voting (*n*)**
• Perform ECG and 24-hour Holter monitoring in patients with Andersen-Tawil syndrome and other patients treated with antiarrhythmic drugs [14].	2+	9	18/18 (100%)	2
• Inform the patient that the procedure might exacerbate and/or precipitate an attack resulting in prolonged post-surgical recovery [67].	2+	9	19/19 (100%)	1
• In patients with *RYR1* and/or *CACNA1S* variants, referral to an MH investigation centre, if possible, is recommended for advice on the risk of MH and use of volatile anaesthetics [44]. In case it is not possible to contact an MH investigation centre before surgery, *e.g.* in case of emergency surgery, use of volatile anaesthetics and/or succinylcholine is contra-indicated in patients with *RYR1* and/or *CACNA1S* variants [70].	2+	9	18/19 (94.7%)	1
• Succinylcholine should be avoided irrespective of the risk of MH [23, 68].	2+	9	18/18 (100%)	2
Intraoperative recommendations				
• Potassium supplementation in patients with paramyotonia congenita can trigger myotonia and should be avoided. In case of fasting, regular control of potassium serum levels is recommended.	3	9	17/17 (100%)	3
• Avoid hypothermia, shivering and agitation as these can cause myotonia [68].	3	9	19/19 (100%)	1
• Avoid high glucose levels and hyperventilation (potentially causing alkalosis) in hypoPP [68].	3	9	16/16 (100%)	4
• Avoid hyperkalaemia and hypoventilation (potentially causing acidosis) in hyperPP.	3	9	16/16 (100%)	4
• Patients treated with mexiletine should not receive class I antiarrhythmics due to the risk of conduction block.	3	9	13/13 (100%)	7
• Succinylcholine and/or acetylcholinesterase inhibitors should be avoided as these may induce myotonia [68].	3	9	18/18 (100%)	2

Table 3: Specific anaesthesia recommendations for myotonic dystrophy type 1 and 2

Preoperative recommendations	SIGN	Median score modified Delphi process	Respondents who scored ≥7	Abstained from voting (*n*)
• Preoperative screening should include ECG, echocardiography and lung function tests (in sitting and the supine position), with review of current medication and therapies (*e.g.* pacemakers, non-invasive ventilation etc.). A neurological examination should be performed to document the degree of muscle weakness, as proximal weakness indicates a greater risk of complications in myotonic dystrophy type 1 [72, 73].	2-	9	19/19 (100%)	1
• Central nervous system (CNS) involvement manifesting as lack of initiative and compliance may complicate pre-operative counselling [74].	2-	9	19/19 (100%)	1
• Consider antacid treatment as aspiration prophylaxis due to gastrointestinal dysmotility [42, 43].	4	7	13/17 (76.5%)	3
Intraoperative:				
• Regional anaesthesia, TIVA and volatile anaesthetics have been used effectively and safely, although rigidity cannot always be prevented [42, 43, 75, 76].	3	9	15/15 (100%)	5
• Use of opioids should be avoided if possible, as there is increased sensitivity to such drugs, with an increased risk of respiratory [77] (and possibly intestinal) complications [72], in case this is not possible, use short-acting opioids.	3	8	14/17 (82.4%)	3
• Pain, cold, electrical or mechanical stimulation and drugs that increase muscle membrane excitability may occasionally trigger myotonia [76] which may be resistant to pharmacological treatment.	3	8.5	18/18 (100%)	2
Postoperative:				
• Avoid the use of opioids if possible [77] [72].	4	9	17/19 (89.5%)	1
• Monitoring should include CO_2 measurements as the hypercapnic response is diminished, also considering that excessive sleepiness may be part of the disease spectrum [74].	4	9	16/19 (84.2%)	1
• Early home discharge is not recommended as there is an increased risk of having prolonged ileus due to intestinal dysmotility.	4	9	16/18 (88.9%)	2
Specific considerations for Myotonic dystrophy type 2				
• The same recommendation as for DM1 as outlined above apply, however, the overall complication rate appears to be lower [78, 79].	2-	9	15/15 (100%)	5
• In a few cases, a postoperative CK rise and increased muscle complaints have been reported [78].	2-	9	14/14 (100%)	6

Table 4: Specific anaesthesia recommendations for muscular dystrophies				
Preoperative recommendations	**SIGN**	**Median score modified Delphi process**	**Respondents who scored ≥7**	**Abstained from voting (*n*)**
• There is a need for a thorough preoperative evaluation: consideration of the exact molecular diagnosis, extent of muscle weakness, and specific assessment of cardiorespiratory involvement depending on the specific genetic background [13, 15-17, 82]. FSHD and OPMD are only exceptionally associated with cardiorespiratory involvement.	2-	9	19/19 (100%)	1
• Pre-operative airway assessment in patients with DMD at an advanced disease stage (i.e. wheelchair-bound patients) requires special attention [21].	2-	9	19/19 (100%)	1
• In DMD patient, CNS involvement manifesting as cognitive deficits, speech problems and psychiatric comorbidities such as anxiety and depression may complicate pre-operative counselling [81].	2+	9	19/19 (100%)	1
• An intravenous hydrocortisone stress regimen should be considered in patients who are or were recently (< 1 year) on a course of corticosteroids (prednisolone ≥ 5mg/day for > 1 month) [60].	2-	8.5	16/18 (88.9%)	2
Intraoperative:				
• AIR seems to be a specific complication of general anaesthesia in dystrophinopathies, especially in the paediatric age. AIR can cause life-threatening hyperkalaemia, and the risk of occurrence is possibly linked to the use of succinylcholine and/or volatile anaesthetics [33, 34]. This is an important consideration in the choice of anaesthesic drugs as part of a comprehensive risk-benefit comparison between alternative techniques for the individual patient.	2+	9	18/18 (100%)	2
• There is no association with MH [33].	2+	9	19/19 (100%)	1
• Impaired primary haemostasis and increased blood loss has been reported in DMD due to impaired vessel reactivity [83, 84].	2-	9	17/17 (100%)	3
• We have not found any reports of AIR associated with dystrophies other than DMD and BMD but cannot exclude the hypothetical risk of AIR when exposed to volatile anaesthetics, particularly in LGMDs where genetic variants affect proteins involved in sarcolemmal stability [33].	4	9	19/19 (100%)	1
Postoperative:				
• Restart oral medication (e.g., steroids in DMD) as soon as possible.	4	9	19/19 (100%)	1

Table 5A: Specific anaesthesia recommendations for congenital muscular dystrophies				
Preoperative recommendations	**SIGN**	**Median score modified Delphi process**	**Respondents who scored ≥7**	**Abstained from voting (*n*)**
• Evaluate the need for fibreoptic tracheal intubation in the presence of craniofacial abnormalities. In some forms with spinal rigidity and markedly reduced neck movement (in particular those due to variants in *LMNA, COL6A, LAMA2,* or *SELENON*) [80], intubation may be difficult.	3	9	17/17 (100%)	3
• Specific attention to potential cardiac involvement should be paid in forms due to variants in *LAMA2,* and the alpha-dystroglycanopathies.	3	9	16/16 (100%)	4
• Respiratory involvement should be considered in patients with variants in *SELENON*, *COL6*, *LAMA2* and the alpha-dystroglycanopathies [80].	3	9	15/15 (100%)	5
Intraoperative:				
• More specific considerations depend on the underlying pathology.	4	9	17/17 (100%)	3
• There is no association with MH.	4	9	18/18 (100%)	2
• We have not found any reports of AIR associated with dystrophies other than DMD and BMD but cannot exclude the hypothetical risk of AIR when exposed to volatile anaesthetics. TIVA and volatile anaesthetics have both been used effectively and safely and should be adapted to the case and surgery in question.	4	8	17/17 (100%)	3
Postoperative:				
• Nutrition needs to be monitored as reduced muscle mass can cause postoperative hypoglycaemia up to several days after surgery [24, 26].	3	9	15/15 (100%)	5
Table 5B: Specific anaesthesia recommendations for congenital myopathies				
Preoperative recommendations				
• Evaluation of the need for fibreoptic tracheal intubation in the presence of craniofacial abnormalities. In some forms with spinal rigidity and markedly reduced neck movement (in particular those due to variants in *SELENON* and *NEB*), intubation may be difficult.	3	9	17/17 (100%)	3
• In X-linked myotubular myopathy (XLMTM), liver function tests and coagulation studies should be performed preoperatively because of potentially associated hepatic involvement [18].	3	9	14/14 (100%)	6
• Cardiac involvement is common in *TTN*-related myopathies and the much rarer forms due to variants in the *MYH7* gene.	3	9	16/16 (100%)	4
• More specific considerations depend on the underlying pathology. Special attention to relevant respiratory involvement should be given in patients with variants in *MTM, NEB, ACTA1, TTN* and *RYR1* (in particular recessive variants) [20, 87]. In contrast to the muscular dystrophies, respiratory impairment may be out of proportion to the degree of limb girdle weakness (for example in *NEB*- and *SELENON*-associated forms) and must be anticipated with a high degree of suspicion [87, 88].	3	9	16/16 (100%)	4
Intraoperative recommendations				
• An increased bleeding tendency due to a coagulopathy has been described in patients with myotubular myopathy [18].	3	9	15/16 (93.8%)	4

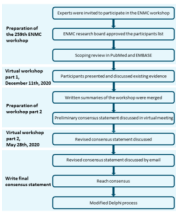
• MH is mainly associated with *RYR1* variants [48] that are found in dominantly or recessively inherited *RYR1*-related myopathies [45] and the King-Denborough syndrome [49]. Less frequently, MH has also has been described in association with variants in *CACNA1S* [47] or *STAC*3 [46]. In case of (presumed) MH-susceptibility, use of volatile anaesthetics and/or succinylcholine is strictly contra-indicated [70].	2+	9	19/19 (100%)	1
• Nutrition needs to be monitored as reduced muscle mass can cause postoperative hypoglycaemia up to several days after surgery. [24, 26]	3	9	17/17 (100%)	3

Table 6A: Specific anaesthesia recommendations for mitochondrial myopathies				
Preoperative recommendations	**SIGN**	**Median score modified Delphi process**	**Respondents who scored ≥7**	**Abstained from voting (*n*)**
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed [25].	4	9	19/19 (100%)	1
• Measurement of blood lactate levels, glucose and serum electrolytes at baseline and during the procedure is important to monitor perioperative metabolic homeostasis.	4	9	19/19 (100%)	1
Intraoperative:				
• Mitochondrial disorders are considered to increase the risk of propofol infusion syndrome [54-56] although there are case series reporting no complications [93, 94]. The cases of propofol infusion syndrome in patients with mitochondrial disorders occurred after 3-5 days of propofol infusion [54-56]. However, propofol infusion syndrome has also been reported after under an hour of infusion in healthy children and after two hours in healthy adults [53].	3	8.5	17/18 (94.4%)	2
• Propofol as an induction agent is safe [95] but should not be used for maintenance of anaesthesia. However, precaution is needed in case of preoperative metabolic deterioration [90].	3	9	16/16 (100%)	4
• Although patients may be hypersensitive, volatile anaesthetics are considered safe [1, 2, 95].	4	9	15/15 (100%)	5
• Etomidate, barbiturates and ketamine are considered safe as induction agents [95].	4	9	15/15 (100%)	5
• Intravenous fluids administered during periods of fasting (especially in paediatric patients) should contain at least 5% glucose (except if the patient is on a ketogenic diet to control seizures). Infusion solutions should be lactate-free, electrolyte solutions containing acetate rather than lactate are preferred [96].	4	9	17/18 (94.4%)	2
• Avoid hypo- and hyperthermia.	4	9	18/18 (100%)	2
Postoperative:				
• In case of post-operative ICU admission and/or mechanical ventilation, the use of propofol should be limited as there is an increased risk for propofol infusion syndrome [54-56].	3	9	18/18 (100%)	2
• Abnormal response to both hypoxaemia and hypercapnia has been observed in Leigh's syndrome [97].	3	9	13/13 (100%)	7
Table 6B: Specific anaesthesia recommendations for muscle glycogen storage diseases				
Preoperative recommendations				
• Avoid circumstances that may increase metabolic burden (e.g. hypo/hyperthermia, hypoglycaemia, hypovolaemia).	4	9	19/19 (100%)	1
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed.	4	9	19/19 (100%)	1
Intraoperative recommendations				
• Volatile anaesthetics are considered safe in all GSDs. Positive *in vitro* contracture tests have been reported in patients with GSDV [98] but these	4	9	19/19 (100%)	1

tests are known to be non-specific in a range of neuromuscular disorders [99]. There are no clinical reports of MH in patients with GSDV.				
• Avoid use of tourniquets, prolonged use of positions associated with rhabdomyolysis and high frequent cycling of intermittent non-invasive blood pressure measurements due to risk of rhabdomyolysis (especially in GSDV).	4	9	19/19 (100%)	1
• Short term TIVA with propofol is considered safe in most GSDs but should be avoided in GSDII, especially in case with severe cardiac involvement.	4	8.5	14/14 (100%)	6
• Monitor glucose, pH, ammonia, lactate, body temperature. Urinary catheter to monitor for myoglobinuria is also recommended.	4	8.5	17/18 (94.4%)	2
Table 6C: Specific anaesthesia recommendations for muscle lipid metabolism disorders				
Preoperative recommendations				
• Avoid circumstances that may increase metabolic burden and provoke catabolic states (e.g. hypo/hyperthermia, hypoglycaemia, hypovolemia).	4	9	20/20 (100%)	0
• Fasting for more than four hours should trigger a glucose drip, to be continued until oral intake is resumed.	4	9	18/18 (100%)	2
• Evaluation for the presence of a cardiomyopathy and coagulopathy (in particular in the presence of hepatomegaly).	4	9	19/19 (100%)	1
Intraoperative recommendations				
• If applicable, propofol should be avoided because of its elevated lipid content in the setting of impaired fatty acid oxidation; however short term use of propofol has been reported in a number of these disorders (MCAD, LCHAD, MTP and VLCAD without complications [100, 101].	3	9	16/16 (100%)	4

Table 7: Risk prediction matrix: multi-system features of patients with neuromuscular disorders.

	Neuromuscular junction disorders	Muscle channelopathies	Myotonic dystrophies	Muscular dystrophies	Congenital muscular dystrophies	Congenital myopathies	Mitochondrial myopathies	Metabolic myopathies	Lipid metabolism disorders
Neurological signs & muscular impairment									
Ataxia									
Cerebral thrombosis									
Cognitive impairment									
Epilepsy									
Encephalopathy									
Myoclonus									
Stroke-like episodes									
Weakness									
Airway									
Aspiration									
Difficult intubation									
Dysphagia									
Macroglossia									
Respiratory									
Respiratory insufficiency									
Cardiac									
Arrythmias									
Cardiomyopathy									
Risk of sudden death									
Other									
Increased bleeding tendency									
Diabetes									
Exercise intolerance									
Hypoglycaemia									
Lactic acidosis									
Rhabdomyolysis									
Spinal deformity									
Malignant hyperthermia susceptibility									
Myotonia									



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