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Workshop report

259th ENMC international workshop: Anaesthesia and neuromuscular disorders 11 December, 2020 and 28–29 May, 2021

LR van den Bersselaar[a,b], S Riazi[c], MMJ Snoeck[a], H Jungbluth[d,e], NC Voermans[b,*], On behalf of the Anaesthesia and Neuromuscular Disorders Working Group[1]

[a] *Department of Anaesthesiology, Malignant Hyperthermia Investigation Unit, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands*
[b] *Department of Neurology, Radboud University Medical Center, Reinier Postlaan 4, P.O. Box 9101, 6500 HB, Nijmegen 6525 GC, the Netherlands*
[c] *Department of Anesthesiology and Pain Medicine, Malignant Hyperthermia Investigation Unit, University Health Network, University of Toronto, Toronto, Canada*
[d] *Department of Paediatric Neurology, Neuromuscular Service, Evelina's Children Hospital, Guy's and St Thomas' Hospitals NHS Foundation Trust, London, United Kingdom*
[e] *Randall Centre for Cell and Molecular Biophysics, Muscle Signalling Section, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom*

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1. Introduction

Patients with neuromuscular disorders are at increased risk of suffering complications related to surgery and general anaesthesia. Complications might be caused by the underlying genetic defect carrying a specific anaesthesia risk; the frequently associated secondary cardiorespiratory complications of the underlying neuromuscular disorder; the increased susceptibility to anaesthetics and neuromuscular blocking agents; difficulties in temperature control and blood glucose regulation due to the reduced muscle mass, or a combination of the above [1,2].

Whilst in recent years comprehensive standards of care have been formulated for the more common neuromuscular disorders such as Duchenne muscular dystrophy (DMD) [3] and spinal muscular atrophy (SMA) [4,5], there is no specific guidance focusing on safe periprocedural anaesthetic management of patients with neuromuscular disorders as a group.

The 259th ENMC international workshop on anaesthesia and neuromuscular disorders was arranged to address this shortcoming. The workshop was initially scheduled for December 2020 in the Netherlands but subsequently held as a virtual workshop because of the ongoing COVID-19 pandemic. The virtual workshop was conducted in three sessions:

1. **Anaesthetic management of various neuromuscular disorders.** This session (December 11th, 2020) aimed to identify and review current knowledge and available evidence concerning the anaesthetic management of patients with neuromuscular junction disorders, muscular dystrophies, channelopathies, myotonic dystrophy, mitochondrial and metabolic myopathies as well as congenital myopathies and congenital muscular dystrophies.
2. **The patient perspective, increasing awareness amongst health care professionals and new developments in malignant hyperthermia (MH).** The aim of this session (May 28th, 2021) was to discuss strategies to increase awareness of anaesthetic issues in neuromuscular disorders and to improve dissemination of knowledge and topical guidelines amongst health care professionals. Furthermore, new developments in MH and the concept ENMC consensus statement on anaesthetic management of patients with neuromuscular disorders were discussed (May 28th, 2021).
3. **Genetic counselling in patients with MH, rhabdomyolysis and congenital myopathies.** This session (May 29th, 2021) focussed on formulating a

* Corresponding author.
E-mail address: nicol.voermans@radboudumc.nl (N. Voermans).
[1] Participants are listed at the end of this article.

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practical proposal for the counselling of patients with congenital myopathies due to *RYR1*, *CACNA1S* and *STAC3* variants and their unaffected family members.

2. PART 1: anaesthesia and neuromuscular disorders – review of current knowledge and available evidence (Virtual, December 11th, 2020)

On December 11th, 2020, 26 scientists and medical doctors, along with two patient representatives from 11 different countries, convened through the Zoom platform for the first session of this 3-part workshop. After a warm welcome from **Alexandra Breukel** on behalf of the ENMC, **Nicol Voermans** (Nijmegen, The Netherlands) and **Marc Snoeck** (Nijmegen, The Netherlands) gave an overview of the preliminary work and the specific aims of this particular ENMC workshop as formulated by the various members of the organizing committee. They emphasized the principal aim of the ENMC Anaesthesia and Neuromuscular Disorders Working Group; raising awareness and increase knowledge of the issues surrounding anaesthesia in neuromuscular disorders amongst neuromuscular specialists, patients and patient organisations. Furthermore, the ENMC Anaesthesia and Neuromuscular Disorders Working Group aims to develop a consensus statement for anaesthesia and neuromuscular disorders specifically targeted at a neurology audience.

In parallel, the European Malignant Hyperthermia Group (EMHG) is preparing a guideline on anaesthesia in myopathies, which will be aimed at anaesthetists and will be published on the EMHG website (www.emhg.org) and in an anaesthesia journal. When finalized, both documents will contain a set of general recommendations concerning anaesthesia and neuromuscular disorders and will give advice for specific groups of neuromuscular disorders including myopathies and neuromuscular junction disorders.

Luc Heytens (Antwerp, Belgium) presented the template for developing an EMHG consensus guideline concerning the anaesthetic management of various myopathies. The guideline is intended for anaesthetists working in a tertiary setting and accustomed to anaesthetising patients with myopathies, but also for those working in general hospitals with less specialist knowledge. Finally, an immediate accessible system is needed for risk assessment and appropriate management of these patients during emergency surgery.

The overall concept of the EMHG consensus guidelines entails three level: Firstly, recommendations that are applicable to all patients with a myopathy in need of anaesthesia or procedural sedation; secondly, recommendations that apply to specific classes of myopathies; and thirdly, recommendations that apply to specific diseases. Preliminary guideline statements and possible controversial questions concerning the latter have already been subjected to the first round of a Delphi process. As for the risks assessment for a particular myopathy the aim is to devise a "risk predicting matrix" based on the "NARCO-SS-acronym" [6] and the model developed by Schieren et al. [2]. The acronym represents a system-based risk assessment tool using the categories **N**eurological, **A**irway, **R**espiratory, **C**ardiovascular and **O**ther, with a subcomponent '**SS**' used for grading Surgical Severity. After evaluation of the results and revision of the recommendations, a second Delphi round will be organized with the aim to finalize the guideline in 2021. Furthermore, for the disease-specific anaesthesia considerations in the many existing orphan diseases the guideline will refer to existing peer-reviewed databases (https://www.orphananesthesia.eu and http://tinyurl.com/PED-RARE).

Luuk van den Bersselaar (Nijmegen, The Netherlands) presented the preliminary results of a literature review on anaesthesia in neuromuscular disorders. PubMed and EMBASE were searched using a scoping review model [7]. Case reports, case series, studies and narrative reviews on this topic were included and the anaesthetic management and peri-operative disease course were reviewed in all cases included. The use of volatile anaesthetics, neuromuscular monitoring, neuromuscular blocking agents and their antagonists were compared between patients with a complicated and an uncomplicated disease course using a Chi-Square test. The literature review identified 192 patients, 30.7% of those had a complicated disease course. The neuromuscular diagnosis was known before surgery in 89.7% of the patients. Succinylcholine and volatile anaesthetics were more frequently used in the patients with a complicated disease course, whereas neuromuscular monitoring and the use of neuromuscular blocking agents, neuromuscular monitoring and neuromuscular blocking agent antagonists were not associated with a complicated disease course. Reversal of residual neuromuscular blockade using sugammadex was associated with an uncomplicated disease course.

After the plenary sessions, the participants separated in two groups with a similar representation of anaesthetists, geneticists and neurologists and both paediatric and adult expertise. The presenters were asked to present their recommendations in a structured format based on the 'three tier system' with 1) general; 2) group-specific; and 3) disease specific recommendations. Presenters had been specifically requested to highlight where specific recommendations differ from 'general recommendations for anaesthesia in myopathies', and to present any further disease specific items in need for attention. Finally, they had been asked to complete the perioperative risk predicting matrix for each condition.

2.1. Parallel session 1

2.1.1. Myotonic dystrophy

Jens Reimann (Bonn, Germany) presented the recommendations for the anaesthetic management of patients with myotonic dystrophy. There are several types of this disorder and patients may present with prominent muscle weakness, respiratory and cardiac manifestations. Myotonic dystrophy type 1 (DM1) patients are usually more severely affected than patients with myotonic dystrophy type 2 (DM2). Proximal muscle weakness [8,9] and a high number of CTG repeats indicate a greater risk of complications

in DM1 patients [8]. Spinal and local anaesthesia are considered relatively safe [8,10]. All anaesthetic drugs should be started at lower than normal dosage [10]. When general anaesthesia is needed, use of short-acting anaesthetics agents is preferable [8]. Total intravenous anaesthesia (TIVA) with propofol, rapid sequence induction (without succinylcholine) and induction with volatile anaesthetics have been used successfully. Anaesthesia can be maintained using TIVA or volatile anaesthetics with close monitoring. If necessary, neuromuscular blockade should be performed with a non-depolarising neuromuscular blocking agent. Neuromuscular monitoring and reversal of residual neuromuscular blockade is recommended [10–12], preferably with rocuronium and sugammadex [12,13]. Succinylcholine, long-acting opiates and cholinesterase inhibitors should be avoided [14].

2.1.2. Muscular dystrophies

Giorgio Tasca (Rome, Italy) presented the recommendations on anaesthetic management in the muscular dystrophies, a wide range of different skeletal muscle disorders with variable clinical severity and various underlying genetic defects and pathophysiological mechanisms. The most common disorders in this group include DMD, Becker muscular dystrophy (BMD), various forms of Limb girdle muscular dystrophy (LGMD), Facioscapulohumeral muscular dystrophy (FSHD) and Oculopharyngeal muscular dystrophy (OPMD). Whilst some of these conditions (for example DMD and certain LGMDs) are commonly associated with cardiorespiratory involvement and/or severe spinal deformities [15], others, for example FSHD and OPMD, are only exceptionally associated with cardiac involvement, and respiratory failure is an issue only in the most severely affected patients. However, these patients might undergo surgery for disease related problems (such as levator palpebrae resection or cricopharyngeal myotomy in OPMD), and careful perioperative monitoring is recommended especially for the most compromised patients.

General recommendations for the anaesthetic management of the patient with a neuromuscular disorder are applicable. Patients with muscular dystrophies do not have an increased risk of MH compared to the general population [16], however, anaesthesia-induced rhabdomyolysis (AIR), which can cause life-threatening hyperkalaemia, is possibly linked with the use of succinylcholine and volatile anaesthetics in dystrophinopathies [17].

Neuromuscular junction disorders

Parallel session 1 ended with a presentation from **Oscar Díaz Cambronero** (Valencia, Spain) on anaesthetic management of (acquired and congenital) neuromuscular junction disorders.

Diseases of the neuromuscular junction comprise a wide range of disorders due to specific genetic variants or induced by pathogenic antibodies, certain drugs or toxins that interfere with the normal signalling between the presynaptic nerve ending and the postsynaptic muscle membrane.

Acquired autoimmune disorders of the neuromuscular junction are most common in adulthood and include myasthenia gravis (caused by antibodies to acetylcholine receptors or to proteins involved in receptor clustering) and Lambert-Eaton myasthenic syndrome (caused by antibodies to the presynaptic voltage-gated calcium channels). Congenital myasthenic syndromes are a phenotypically heterogeneous group of neuromuscular disorders with impaired neuromuscular transmission due to a variety of genetic defects and typically presenting in infancy and childhood [18]. Facial muscles, including those controlling the eyelids, eye movements, chewing and swallowing, are prominently affected. Some patients may experience episodes of respiratory crisis often triggered by pyrexia and/or infection. If possible, surgery should only be performed when the condition is stable, and the patient is on a low dose of immunomodulatory medication. Patients with neuromuscular junction disorders are at risk for specific peri–operative complications such as myasthenic crisis, cholinergic crisis and cholinergic excess [19]. Short-acting sedatives and hypnotics agents are preferred to minimize respiratory depression on emergence from anaesthesia. There is no contraindication for halogenated agents. The use of neuromuscular blocking agents must be avoided if possible, but if needed, rocuronium and reversal with sugammadex ought to be considered as first choice [20]. Patients may be particularly sensitive to non-depolarizing neuromuscular blocking agents [21–23].

2.2. Parallel session 2

2.2.1. Mitochondrial and metabolic myopathies

Nicoline Løkken (Copenhagen, Denmark) gave an overview of the anaesthetic management of mitochondrial and metabolic myopathies, she was supported by **Luc Heytens** (Antwerp, Belgium). Primary mitochondrial disease is a heterogeneous group of disorders, with some patients having primarily skeletal muscle involvement consistent with a mitochondrial myopathy. In addition to muscle symptoms such as exercise intolerance and muscle fatigue, patients can present with signs and symptoms of multisystem involvement, including neurological features such as epilepsy, ataxia, encephalopathy and stroke-like episodes, as well as respiratory and cardiac disease manifestations. Other potentially concerning issues are metabolic disturbances (e.g. lactic acidosis, hypoglycaemia, diabetes), and spinal deformities in those with prominent neuromuscular involvement [24].

General advice for the anaesthetic management of patients with a mitochondrial myopathy should include avoidance of major metabolic changes whenever possible. Volatile anaesthetics are safe in low doses, bearing in mind that patients may have increased sensitivity [25]. Propofol infusion syndrome has been reported but only after prolonged infusion [26], thus short term propofol use may be considered relatively safe. The following adjuvant drugs should be avoided: valproate acid (especially in patients with confirmed *POLG* variants and those with

genetically unresolved mitochondrial myopathies), topiramate and metformin (because of the risk of lactic acidosis) and selected antibiotics: aminoglycosides, linezolid, azithromycin, erythromycin.

Metabolic myopathies other that primary mitochondrial disorders can be subcategorized as muscle glycogenoses (or glycogen storage disorders, GSDs) and muscle lipid metabolism disorders. Most muscle glycogenoses disorders almost exclusively affect skeletal muscle, however, GSD type II requires special attention as patients may have severe multi-system involvement, including cardiac and respiratory involvement [24]. Some muscle GSDs have increased susceptibility to muscle stress contractures, rhabdomyolysis and renal failure. Therefore, any situation that may elicit general and specific myopathic metabolic stress (for example, catabolic states including prolonged fasting, use of tourniquets, etc.) should be avoided.

Regional anaesthetic techniques are considered safe and should be chosen when possible (especially in GSD type II). Volatile anaesthetics in judicious doses are considered safe in all GSDs except maybe GSDV, in whom positive caffeine/halothane contracture tests have been obtained [27]. However, in view of the absence of clinical reports, the relevance hereof is doubtful as the caffeine/halothane contracture test is not validated to test patients with myopathies. Patients with a neuromuscular disorder may be prone to a false positive test due to a non-specific contracture in response to MH triggering agents [28]. Short term TIVA with propofol is safe in most but should be avoided in GSDII, especially in case with severe cardiac involvement [29].

Disorders of lipid metabolism can also manifest in organs other than muscle, in particular in the heart with cardiomyopathy and arrythmias. Furthermore, rhabdomyolysis, recurrent muscle pain, hypoketotic hypoglycemia, acidosis, elevated ammonia, hepatomegaly, coagulopathy, muscle weakness have all been reported [24]. Regional and volatile anaesthetics can be used safely. There is a theoretical rationale for the avoidance of propofol because of its elevated lipid content in the context of impaired fatty acid oxidation, however, propofol has been shown to be safe for short term use in a number of these disorders including *MCAD*, *LCHAD*, *MTP* and *VLCAD* [30,31].

2.2.2.Channelopathies

Juan Jesus Vilchez (Valencia, Spain) presented recommendations for the anaesthetic management of the skeletal muscle channelopathies, a group of rare heterogeneous diseases, characterized by alterations in muscle fibre excitability due to variants in genes encoding specific chloride (ClC-1), sodium (NaV1.4), calcium (CaV1.1), and several potassium channels (Kir2.1, Kir2.6, and Kir3.4). The clinical manifestations are often striking, with myotonia or periodic paralysis as the most prominent manifestation. An essential feature of these disorders is fluctuation of symptoms that is strongly affected by environmental and other factors such as exercise, changes in temperature, pain, emotional disturbance, fasting or abnormal serum potassium concentrations [32].

Evidence of anaesthetic complications in channelopathies is mainly derived from retrospective studies and case reports. In a recent survey up to 31% of patients reported worsening of symptoms and prolonged recovery time after general anaesthesia [33]. Attacks of periodic paralysis related to hypokalaemia and hyperglycaemia following anaesthesia have also been reported [33]. In case of (prolonged) fasting, regular measurement of glucose and potassium serum levels is therefore recommended. It is also recommended to avoid hypothermia, shivering and agitation as this can cause an increase in myotonia.

2.2.3. Congenital myopathies and congenital muscular dystrophies

Andrea Klein (Bern and Basel, Switzerland) presented on the anaesthetic management of congenital myopathies and congenital muscular dystrophies. She was supported by **Ron Litman** (Philadelphia, USA). Congenital myopathies and congenital muscular dystrophies are two groups of early-onset neuromuscular disorders with considerable clinical overlap, including shared features of early-onset proximal, axial and facial weakness with slow progression, and orthopaedic problems including frequent contractures and scoliosis. Congenital myopathies are a heterogeneous group of disorders, with more than 20 genes involved encoding proteins implicated in skeletal muscle calcium homeostasis, excitation–contraction coupling, thin–thick filament assembly and interactions. Genes associated with congenital muscular dystrophies encode for proteins of the plasma membrane–extracellular matrix interface, proteins involved in O-glycosylation of the dystrophin-associated glycoprotein (DAG) or intracellular proteins. Depending on the underlying disease, cardiac, respiratory and, less frequently, central nervous system involvement, may be prominent [15]. Relevant respiratory involvement should be considered in patients with variants in *SELENON*, *MTM*, *NEB*, *TTN*, recessive (and *de novo*) *RYR1*, *COL6*, and *LAMA2* as well as the alpha dystroglycanopathies. Cardiac involvement may be prominent in *TTN*, *MYH7*, *LAMA2* and alpha dystroglycanopathies. In some patients with spinal rigidity and associated markedly reduced neck movement, intubation may be difficult (for example in patients with variants in *LMNA*, *LAMA2*, *SELENON* and *NEB*). An increased bleeding tendency has been reported in an animal model with an *RYR1* variant relevant for MH and in older patients with *MTM* variants due to a potentially associated coagulopathy [34,35]. As in other neuromuscular disorders, careful temperature management and lower doses of muscle relaxants are necessary during operative procedures due to the reduced muscle mass [36], which may also cause hypoglycaemia [37,38]. MH is associated with certain *RYR1* variants found in dominantly or recessively inherited *RYR1*-related myopathies such as Central Core Disease (CCD), King-Denborough syndrome (KDS) or exertional rhabdomyolysis (ERM) [39–41]. Less frequently, MH has also been described in association

with dominant variants in *CACNAS1* [42,43] or recessive variants in the *STAC*3 gene [44]. Inhalation anaesthesia and succinylcholine may cause rhabdomyolysis (AIR) and hyperkalaemia in congenital muscular dystrophies [16,45]. Succinylcholine should therefore be avoided; non-depolarising neuromuscular blocking agents can have a delayed effect and the dose needs to be reduced. TIVA and regional anaesthesia is considered safe.

2.2.4. Discussion and conclusion

Marc Snoeck (Nijmegen, The Netherlands) summarized the conclusions and planned practical steps from the parallel sessions and outlined the roadmap to an ENMC consensus statement on anaesthetic management of neuromuscular disorders.

Subsequently, **Heinz Jungbluth** (London, UK) presented a preview of the third part of the workshop '*Genetic counselling in patients with MH, rhabdomyolysis and congenital myopathies'*. The increasing diagnostic use of next generation sequencing in patients with unresolved neuromuscular disorders (but without a personal or family history of MH) has led to the increasing identification of *RYR1*, *CACNA1S* and *STAC3* variants of uncertain significance. There is currently no structured approach how to ascertain such incidentally identified (in particular *RYR1*) variants with regards to their associated MH risk, resulting in considerable counselling challenges as illustrated by a number of clinical vignettes presented in this part of the workshop.

3. PART 2: new developments in the field of malignant hyperthermia, increasing awareness, and the ENMC consensus statement on anaesthetics management of patients with neuromuscular disorders (Zoom, May 28th, 2021)

On May 28th, 2021 the workshop participants convened through Zoom for part two of the 259th ENMC workshop to discuss new developments in the MH field, as well as the ongoing efforts to increase awareness of this topic amongst health care professionals and patients. Furthermore, the concept ENMC consensus statement concerning the anaesthetic management of patients with neuromuscular disorders, prepared after the first part of the workshop was discussed to reach consensus

3.1. New developments in the field of MH

This session was dedicated to new developments in the MH field and was chaired by **Luc Heytens** (Antwerp, Belgium). Several participants are members of the EMHG and/or are affiliated to MH investigating units throughout the world and are therefore in an excellent position to give an update on MH and related neuromuscular disorders.

Anna Hellblom (Lund, Sweden) presented on the differences and similarities between MH and AIR, two emergencies that may occur during general anaesthesia. Although both MH and AIR share the common feature of rhabdomyolysis, a hypermetabolic reaction with sympathetic nervous system activation preceding the rhabdomyolysis appears to be specific for MH [46,47]. In both conditions, the rhabdomyolysis leads to release of intracellular components into the circulation, resulting in hyperkalaemia, myoglobinuria with a risk of developing acute kidney injury and potentially cardiac arrhythmias and even cardiac arrest [47,48].

The rhabdomyolysis in MH and AIR have a different pathophysiology. In MH, rhabdomyolysis is caused by the uncontrolled release of calcium from the sarcoplasmic reticulum when triggering agents act on the sensitized ryanodine receptor type 1 (RyR1) in susceptible individuals. In AIR, the main mechanism is thought to be sarcolemmal instability, possibly in combination with reduced mitochondrial capacity, that will lead to an increased susceptibility to rhabdomyolysis [47]. AIR usually occurs in – often yet undiagnosed – patients with DMD or BMD, with reduced or absent dystrophin expression thought to cause the instability [16].

Both conditions have the same triggering agents, but in the perioperative setting, there are several other factors that may contribute to the development of AIR, for example steroids, propofol, ketamine, surgery, fasting, excessive muscle activation (for example through agitation or anxiety) or impaired muscle repair due to hypoxaemia, ischemia, and acidosis [49]. No consensus could be established amongst the workshop participants regarding the short-term use of volatile anaesthetics in patients with muscular dystrophies.

Francis Veyckemans (Lille, France) presented a practical approach on how to anaesthetise a child with an unspecified myopathy. Children with a suspected muscle disease frequently undergo anaesthesia to establish a diagnosis (e.g. for muscle biopsy, muscle MRI, etc.), to palliate its consequences (for example, gastrostomy insertion) or for unrelated indications. In addition to providing safe anaesthesia and analgesia, the anaesthetist's specific goal in a child with an undiagnosed myopathy is to avoid the following rare complications [50]:

- MH (associated with *RYR1*, C*ACNA1S* and *STAC3*-related myopathies) [48,51,52].
- AIR (associated with genetic disturbances of the dystrophin-glycoprotein complex, in particular DMD) [16].
- Propofol-Related Infusion Syndrome (associated with mitochondrial myopathies) [26].

To avoid these complications, regional anaesthesia or general anaesthesia with alternative drugs such as ketamine and dexmedetomidine may be considered [50]. Succinylcholine should be avoided if possible, in suspected muscle disease because of its recognized role as a strong trigger of MH, AIR and hyperkalaemia in these patients [16,50]. If neuromuscular blockade is needed in such patients, a non-depolarising neuromuscular blocking agent should be used instead with the dosage titrated based on neuromuscular monitoring; rocuronium might be the agent of first choice as it can be easily reversed with sugammadex [50].

In addition to the usual considerations, the pre-operative work-up should include baseline blood creatine kinase (CK) and lactate levels, respiratory function tests and an echocardiographic examination to rule out a subclinical cardiomyopathy. Furthermore, a multidisciplinary approach is essential as the neuromuscular differential diagnosis provided by a paediatric neurologist trained in neuromuscular disorders is of utmost importance with regards to the specific anaesthetic strategy [50]. A pragmatic anaesthetic approach to a child with an unspecified myopathy could be:

- if a myopathy is suspected (isolated hypotonia of presumably neuromuscular origin and high CK levels), total intravenous propofol-based anaesthesia might be the first choice to avoid AIR and MH.
- if a metabolic disease is suspected (hypotonia in a context of multiorgan involvement and metabolic crises with elevated baseline blood lactate), volatile anaesthetics might be the first choice.

Unfortunately, there is a large grey area between these two classes of neuromuscular disorders. Moreover, genetic myopathies carrying a specific MH risk may have entirely normal CK levels. Furthermore, as not every exposure to a halogenated agent or propofol results in MH, AIR or PRIS, respectively, a history of previous uneventful exposure to these agents is of little predictive value.

Phil Hopkins (Leeds, UK) presented on the overlapping mechanisms of MH and exertional heat illness (EHI). Exertional heat illness is a consequence of heat generated by sustained muscular activity with the pathology resulting from retained heat (hyperthermia), the body's adaptive response to dissipate excess heat, or a combination of the two. Thirty years ago his group demonstrated a familial skeletal muscle abnormality in two survivors of exertional heat illness: they proposed that the abnormality was similar (affecting calcium regulation) but perhaps not identical to that predisposing to the development of MH under anaesthesia [53]. Subsequent reports have suggested that variants in the *RYR1* gene may be implicated in exertional heat illness as well as MH.

In 2020 his group published the results of sequencing a panel of genes, including *RYR1* in a cohort of 64 survivors of exertional heat illness who had either required hospital admission (because of cerebral dysfunction or organ damage) or developed rhabdomyolysis [54]. The majority were military personnel who were subsequently shown to have continued heat intolerance when exercised in a controlled thermal environment. Thirty-four percent of their cohort had an abnormal in vitro contracture test (IVCT) and there was a higher prevalence of *RYR1* variants in these patients [27% (95% confidence interval 13–48%)] than those who tested MH normal (MHN). This compares to a prevalence of *RYR1* variants of 76% [95% confidence interval 72–79%] in MH patients. Their data included the second report of *RYR1* p.Ile3253Thr associated with exertional heat illness: this variant has previously been implicated in congenital myopathy and also has been found in an MH susceptible patient presenting with myalgia and idiopathic hyperCKaemia. They also found *RYR1* p.Thr3711Met to be associated with EHI: this variant has been previously reported in two MH susceptible individuals who respectively presented with rhabdomyolysis and myalgia. Their data further suggest that combinations of defects in genes involved in calcium homeostasis, oxidative metabolism and membrane excitability may be implicated in EHI and ERM.

Heinz Jungbluth (London, UK) presented on the evolving relationship between MH and ERM, two often *RYR1*-related manifestations with considerable clinical and pathophysiological overlap. Whilst *RYR1*-related MH is a primarily genetically determined condition, an additional environmental contribution is suggested by its close similarities with *RYR1*-related ERM, and the currently unresolved discrepancy between risk genotypes (estimated at 1 in 2000) and the actual frequency of MH (estimated at 1 in 15,000–75,000) [48]. Prompted by their previous observation of a fatal MH event in an individual exposed to volatile anaesthetics within 72 h of strenuous exercise [55], he and his collaborators collected 41 additional cases from 5 international MH centres (Toronto, Antwerp, Lund, Nijmegen and Melbourne) in whom the MH event had been associated with strenuous exercise and/or pyrexia within 72 h before administration of the triggering agent. Emergency surgery, use of succinylcholine as well as trauma and acute abdomen as surgery indications were identified as additional risk factors (manuscript currently under review). These findings suggest that MH is a compound event due to a combined effect of genetic and non-genetic factors and have important implications for perioperative anaesthetic management.

Henrik Rueffert (Leipzig, Germany) presented on dantrolene as a treatment for MH and rhabdomyolysis. Dantrolene was primarily approved by the US Food and Drugs Administration (FDA) for the (intravenous) treatment of MH [46] and as an oral medication for upper motor neuron disorders with increased spasticity, including stroke, spinal cord injury, cerebral palsy and multiple sclerosis [56]. Off-label use has included severe manifestations of the neuroleptic malignant syndrome [57], and treatment of individual cases of cerebral vasospasm [58] and catecholaminergic polymorphic ventricular tachycardia[59]. It has also been considered as a potential treatment for Alzheimer's disease [60].

In skeletal muscle cells, dantrolene inhibits the release of calcium into the cytosol, either by directly antagonizing RyR1 and/or by indirectly affecting proteins that regulate RyR1. Although the precise mechanism of action remains controversial. Furthermore, dantrolene might have an additional cytoprotective effects by decreasing intracellular calcium concentration and thus reducing production of oxygen radicals, nitric oxide and pro-apoptotic factors [61]. There are case reports suggesting that dantrolene may be effective a treatment for rhabdomyolysis related to septic conditions or severe COVID-19 infections [62].

The effect of dantrolene in MH is based on the inhibition of uncontrolled calcium release from the sarcoplasmic reticulum into the cytosol by antagonizing the RyR1,

thus indirectly abolishing the hypermetabolic pathways that are characterized by excessive oxygen and adenosine triphosate (ATP) consumption, carbon dioxide, lactate and heat production. Although dantrolene is highly effective, the first step in successful MH treatment is not to give dantrolene, but cessation of exposure to the triggering agent [46].

Rhabdomyolysis has a different pathophysiological pathway. The depletion of ATP within the muscle cell leads to an increase in intracellular calcium and myocyte death. Dantrolene seems to be able to restore calcium homeostasis. Combined with its cytoprotective and anti-inflammatory effects, dantrolene may diminish cell death if the underlying disorder that is causing rhabdomyolysis can successfully be treated. Furthermore, dantrolene has been used successfully as a prophylactic treatment for *RYR1*-related ERM in severely affected patients [63].

3.2. Increasing awareness, the patient perspective, and dissemination of knowledge

The second session was chaired by **Henrik Rueffert** (Leipzig, Germany). First, **Nicol Voermans** (Nijmegen, The Netherlands) presented the medical aspects of a semi-professional cyclist's story who needed to end his cycling career because of recurrent episodes of exercise-induced rhabdomyolysis related to an *RYR1* variant. A recording of the patient's perspective on his story was disseminated amongst the participants**.**

Luuk van den Bersselaar (Nijmegen, The Netherlands) then presented the preliminary results of a questionnaire study targeted at anaesthesiologists and neurologists and concerning current practice in peri-operative care for patients with neuromuscular disorders. A total of 164 relevant health care professionals from Canada, The Netherlands and the United Kingdom participated in this study, amongst those 66% were anaesthesiologists and 34% were neurologists. Half of the participants worked in a general and the other half in an academic hospital. Daily practice in peri-operative care for the patient with neuromuscular disorders appeared to be highly variable. Only 59% of anaesthesiologists and only 28% of neurologists considered training of anaesthesia residents on this topic as good or very good. Furthermore, the questionnaire study revealed that most neuromuscular patients needing surgery under general anaesthesia were not discussed at a multi-disciplinary meeting with a neurologist and anaesthesiologist.

Future strategies to improve peri-operative care for patients with neuromuscular disorders should therefore involve the promotion of multidisciplinary meetings with relevant professionals on a regular basis and improve training of residents concerning this topic.

Henrik Rueffert (Leipzig, Germany) presented the benefits of and difficulties with anaesthesia alert cards and SOS devices in an acute care setting in Germany. The activation of the German medical emergency system is based on a national emergency telephone number (112) that ensures a direct contact with a call centre. After a structured query about the nature of the emergency, the operator will mobilize the emergency rescue service. After arrival and the initial treatment, the emergency team needs to read out the information from the patient's electronic health card, however, only personal identification data and the insurance policy number are recorded on this card.

SOS devices may be helpful in an emergency and can send out an alarm call to an emergency control centre very fast. These devices are easy to use and might be the preferred choice in elderly patients, however, the device must be worn permanently and in case of emergency, the holder must be conscious for at least a few seconds to press the help button in order for the system to be activated.

In Germany, Medical Alert Cards are used in several formats. They carry lifesaving information for the benefit of first responders, save time when obtaining the medical history and may prevent severe drug interactions and/or prevent avoidable complications arising from known allergies. However, the cards frequently get lost or the information on it is interpreted incorrectly.

An In Case of Emergency (ICE)-app on a smartphone is a more recently introduced option that enables to contact the family of the owner, however, this concept has been criticized because contacting relatives of an injured patient is a highly sensitive task and that should not be left to apps or other impersonal electronic devices [64,65].

In modern electronic patient files abnormal laboratory results as well as specific risks or co-morbidities relevant for the acute care setting are highlighted (e.g. displayed in red) and are useful for instant and easy information of the emergency physician. However, this advantage may be compromised in the presence of many abnormal results and co-morbidities, both common in an acute care setting.

In general, electronic patient files including all relevant medical information are increasingly used, but safe and quick access in case of an emergency with an unconsciousness patient as well as issues surrounding privacy law remain challenging.

Finally, **Charlotte van Esch** (Utrecht, The Netherlands) presented on the ALERT project initiated by the Dutch patient organisation for neuromuscular disorders (Spierziekten Nederland). She explained the process of developing and implementing emergency warning cards for patients affected by neuromuscular disorders. In general, emergency health care professionals are not necessarily familiar with patients with neuromuscular disorders, which is of great concern considering that standard emergency procedures may be dangerous or even fatal for these patients. The Dutch patient organization for neuromuscular diseases therefore started the ALERT project, with the specific aim to inform emergency health care professionals of the vital and specific issues that affect neuromuscular patients in emergency situations.

Aided by patients and emergency health care professionals, the first step of the project was to identify the most pressing problems surrounding the emergency care. Patients with neuromuscular disorders experience problems with respiratory care on the intensive care unit, prescription of medication in

emergency situations, anaesthesia and antibiotics. Emergency health care professionals frequently do not know how health care for patients with neuromuscular disorders is organized and which specialists they can contact. In the second phase of the project, emergency warning cards were developed again with the help of patients and relevant health care professionals. Specific ALERT cards for health care professionals were developed for the following neuromuscular disorders:

- DMD
- FSHD
- Myasthenia gravis
- DM1
- SMA
- Patients with another neuromuscular disorder with specific respiratory care needs

Furthermore, additional SOS cards were developed for patients. These cards are conveniently shaped to fit inside a wallet and outline key recommendations and precautions that emergency health care professional need to know. SOS cards were developed for:

- DMD
- FSHD
- Myasthenia gravis
- DM1
- SMA
- Patients with another neuromuscular disorder with specific respiratory care needs
- *RYR1*-related myopathies

The cards are easily accessible for emergency health care professionals and patients (https://spoed.spierziekten.nl). The project was funded by the Prinses Beatrix Spierfonds.

3.3. ENMC consensus statement for anaesthetic management of patients with neuromuscular disorders

The last session was dedicated to the draft ENMC consensus statement for the anaesthetic management of patients with neuromuscular disorders. The participant discussed the risk assessment tool for the ENMC anaesthesia consensus statement, and **Nicol Voermans** (Nijmegen, The Netherlands) and **Marc Snoeck** (Nijmegen, The Netherlands) presented the timeline for the preparation of a final consensus statement. Furthermore, possibilities to start multi-centre research and prospective data collection in a common database focussing on the anaesthetic management of patients with neuromuscular disorders were discussed.

4. PART 3: genetic counselling in patients with malignant hyperthermia, rhabdomyolysis and congenital myopathies (Zoom, May 29th, 2021)

On May 29th, 2021 the workshop participants convened through Zoom for part three of the 259th ENMC International Workshop on anaesthesia and neuromuscular disorders, focussing on genetic counselling in patients with MH, rhabdomyolysis and congenital myopathies. The increasing diagnostic use of next generation sequencing in patients with unresolved neuromuscular disorders (but without a personal or family history of MH) has led to the increasing identification of *RYR1*, *CACNA1S* and *STAC3* variants of uncertain significance, posing a substantial counselling challenge.

John Rendu (Grenoble, France) presented on the already known and new genes associated with MH. Until recently only a few loci have been linked to MH but fully classified pathogenic variants were identified in only two genes, *RYR1* and *CACNA1S*. *RYR1* variants are involved in 50–70% of MH cases [66], emphasizing the crucial role of RyR1 hypersensitivity in the pathophysiology of MH. Furthermore, *RYR1* variants are responsible for a wide spectrum of neuromuscular diseases ranging from MH susceptibility to fetal akinesia [67,68]. To date, over 200 *RYR1* variants have been identified in MH patients but only 48 *RYR1* variants and two *CACNA1S* variants have been classified as pathogenic for MH by the EMHG according to their very stringent criteria (www.emhg.org/diagnostic-variants). Due to the complex structure of the RyR1, classification of *RYR1* variants is challenging; the IVCT is currently the only accepted test to confirm or rule out MH susceptibility in case of an *RYR1* variant of unknown significance [52].

CACNA1S variants are identified in 1% of the MH cases [69]. Other genes have also been linked to MH but only for *STAC3* there is strong mutational evidence for an association with MH. *STAC3* is associated with the Native American Myopathy/Baily-Bloch congenital myopathy [70].

Kathryn Stowell (Palmerston North, New Zealand) presented on pathogenicity prediction for *RYR1* variants in MH susceptibility. The guidelines for classifying genetic variants associated with human disorders developed by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) have been updated for *RYR1* and MH by the ClinGen Variant Curation Expert Panel (VCEP) [71]. The EMHG executive committee previously developed a scoring matrix specific for MH susceptibility based on the original ACMG/AMP guidelines together with current diagnostic parameters [52]. Both systems can be used to score variants into five categories for MH susceptibility: pathogenic, likely pathogenic, variant of unknown significance, likely benign and benign. The two systems were compared to classify a limited number of variants in each of the five categories. This required an assessment of the literature, amino acid sequence conservation, prevalence of variants in the population, associated clinical reactions, segregation of caffeine halothane contracture test (CHCT)/IVCT phenotype in affected families and computational evidence. Most variants could be classified within the same category by both methods. Combinatorial curation methods are useful in identifying pathogenic and likely pathogenic *RYR1* variants. The EMHG scoring matrix places an emphasis on functional analysis in order to classify a variant as pathogenic. The VCEP criteria are less restrictive

as a larger number of combinatorial criteria can be considered. Use of either method could enable more widespread predictive DNA testing.

Klaus Dieterich (Grenoble, France) presented on genetic counselling in MH and summarized current challenges and limitations. Genetic testing for hereditary anomalies or risk factors has both individual and family consequences. The individual has the choice to have a genetic test or not, and the test result remains confidential. Nevertheless, the tested individual has a moral obligation towards family members to inform them about relevant test results. It is therefore paramount that patients should be counselled on the limits of the test and its possible results and consequences before any genetic test is performed. The principle of self-determination prevails in adults even in the absence of immediate consequences after the test. In contrast, minors should only undergo genetic testing if there is a direct benefit for them in terms of therapeutic or preventive measures [72].

MH susceptibility should be regarded as a substantial risk to develop the disease but without certainty to develop it and can therefore be regarded as predictive rather than pre-symptomatic testing. Testing should be performed at the earliest age at which preventive measures are useful [72].

In case of autosomal recessive *RYR1*-related myopathies, predictive testing for MH is concurrent to the carrier status testing in family members. These risks need both to be addressed in a 2-in-1 genetic counselling. In case of autosomal dominant *RYR1*-related myopathies with MH susceptibility, counselling should focus on the myopathy first, then the potentially associated MH risk. Genetic testing and counselling for MH susceptibility needs to be performed in a specialized and multidisciplinary network.

Luuk van den Bersselaar (Nijmegen, The Netherlands) presented the preliminary results of a retrospective study reviewing the referral criteria for MH diagnostics between 2010 and 2019 in four MH units. An increasing number of patients without a (family) history of anaesthetic adverse event were referred to MH units during the study period. Those were mainly patients with *RYR1*-related myopathies, recurrent or exertional rhabdomyolysis and patients with *RYR1* variants incidentally detected during neuromuscular diagnostics with an unresolved neuromuscular phenotype possibly related to the *RYR1* variant. Currently, there is no well-defined strategy how to counsel these patients. Up to 24% of the patients referred to MH units without a history of anaesthetic adverse events were tested MHS. Since referral criteria are changing and a significant proportion of these patients are tested MHS, MH units do need a strategy to counsel these patients.

Heinz Jungbluth (London, UK) presented a concept ENMC consensus statement concerning genetic counselling in *RYR1*-related disorders, with special emphasis on the potentially associated malignant hyperthermia risk. Whilst the relationship between diagnostic MH variants, IVCT and MH susceptibility is relatively well established, there is a substantial degree of uncertainty regarding the MH risk and the role of the IVCT as a predictive test in the more recently recognized recessive *RYR1*-related myopathies, and *RYR1*-related episodic phenotypes other than MH such as exertional myalgia and rhabdomyolysis. There is currently also no consensus regarding a standardized approach to the pathogenicity ascertainment of the increasing number of *RYR1* variants incidentally identified on WES/NGS. One of the aims of the ENMC workshop was to reach a consensus recommendation on which patients need to be counselled and tested for the risk of MH and/or referred for family testing. A proposal for genetic counselling in different clinical contexts was provided and a number of illustrative clinical cases to highlight the most pertinent questions were presented. The comments raised during the discussion will be used to revise the recommendations, which will subsequently be sent out for final approvement and published in a separate document.

5. Conclusions, outcomes and deliverables from the workshop

The virtual meetings arranged as part of this workshop were a great opportunity to exchange knowledge between scientists and physicians working in the fields of anaesthesia, neuromuscular disorders and genetics. Although there have been few large retrospective studies on the topic of anaesthesia in neuromuscular disorders, most evidence is based on small case series and expert opinion, subject of a review article currently prepared by the workshop organisers. Furthermore, expert opinion based ENMC recommendations on anaesthesia and neuromuscular disorders can be of value for health care professionals in the field of anaesthesia, neuromuscular disorders and genetics, and is currently summarized as a consensus statement by workshop participants.

In addition, workshop participants agreed that a shared database would be of great value for prospective data collection on this topic and will jointly explore strategies how to implement such a database.

Another important topic addressed during this workshop was the genetic counselling in patients with *RYR1*-related neuromuscular phenotypes. Genetic counselling on the risk of MH in these patients remains challenging because of the increasing number of rare *RYR1* variants. The workshop participants will work on a consensus statement concerning genetic counselling in patients with *RYR1*-related and other congenital myopathies.

Lastly, the patient representatives present at the workshop emphasised the importance of awareness among health care professionals and patients concerning the challenges surrounding anaesthesia in individuals with neuromuscular disorders. Projects such as the ALERT project from the Dutch neuromuscular disorders patient organisation might help resolve problems faced by patients with neuromuscular disorders in medical emergency situations. The Dutch neuromuscular disorders patient organisation will evaluate the project in the upcoming years. This will probably give useful information to improve the emergency warning cards system

and may be helpful for future implementation of similar systems in other countries.

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Workshop participants

Börge Bastian, Leipzig, Germany
Luuk R van den Bersselaar, Nijmegen, the Netherlands
Martina Cornel, Amsterdam, the Netherlands
Oscar Díaz Cambronero, Valencia, Spain
Klaus Dietrich, Grenoble, France
Charlotte van Esch, Utrecht, the Netherlands
Francesca Forzano, London, UK
Robyn Gillies, Melbourne, Australia
Anna Hellblom, Lund, Sweden
Luc Heytens, Antwerp, Belgium
Phil Hopkins, Leeds, UK
Stephan Johannsen, Wurzburg, Germany
Heinz Jungbluth, London, UK
Erik-Jan Kamsteeg, Nijmegen, the Netherlands
Andrea Klein, Basel and Bern, Switzerland
Ron Litman, Philadelphia, USA
Nicoline Løkken, Copenhagen, Denmark
Tino Münster, Regensburg, Germany
Jens Reimann, Bonn, Germany
John Rendu, Grenoble, France
Sheila Riazi, Toronto, Canada
Henrik Rueffert, Leipzig, Germany
Helga CA Silva, Sao Paulo, Brazil
Marc MJ Snoeck, Nijmegen, The Netherlands
Maria Soller, Stockholm, Sweden
Kathryn Stowell, Palmerston North, New Zealand
Giorgio Tasca, Rome, Italy
Francis Veyckemans, Lille, France
Juan Jesus Vilchez, Valencia, Spain
Nicol C Voermans, Nijmegen, The Netherlands

Declaration of Competing 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.

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We would like to dedicate this workshop report to the late Professor Ron Litman, an internationally distinguished paediatric anaesthetist, and a respected educator with various expertise including medication safety and endless contributions to the field of Malignant Hyperthermia. Professor Litman participated and contributed to the first session of the workshop.

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Several authors of this publication are members of the Radboudumc Center of Expertise for neuromuscular disorders (Radboud-NMD), Netherlands Neuromuscular Center (NL-NMD) and the European Reference Network for rare neuromuscular diseases (EURO–NMD).

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