Malignant hyperthermia: still an issue for neuromuscular diseases?

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Purpose of review
We will give an overview of neuromuscular disorders that can be linked with malignant hyperthermia or malignant hyperthermia-like reactions, and suggest an appropriate approach to interpret the risks.

Recent findings
An increasing number of neuromuscular phenotypes have been linked to malignant hyperthermia susceptibility (MHS). This is for an important part due to the highly variable phenotype associated with mutations in the ryanodine receptor 1 gene (*RYR1*), the gene most frequently associated with MHS. A *RYR1*-mutation or a clinical *RYR1*-phenotype does not automatically translate in MHS, but precautions should be taken nonetheless. In addition, several other genes and phenotypes are now considered to be associated with MHS. In contrast, several neuromuscular diseases that were long thought to be linked to MHS are now known to cause malignant hyperthermia-like reactions instead of malignant hyperthermia. This is highly relevant as not only the given preoperative advice differs, but also acute treatment.

Summary
This review provides a summary of current evidence linking certain neuromuscular diseases to malignant hyperthermia or malignant hyperthermia-like reactions. We provide a guide for the clinician, to determine which patients are at risk of malignant hyperthermia or malignant hyperthermia-like reactions perioperatively, and to ensure adequate treatment in case such a severe acute complication occurs.

Keywords
anesthesia-induced rhabdomyolysis, dantrolene, malignant hyperthermia susceptibility, malignant hyperthermia-like reactions, myopathies

INTRODUCTION

The first case of malignant hyperthermia was described in 1960 in a young man who developed hyperthermia, tachycardia and a drop in blood pressure 10 min after general anesthesia with halothane [1]. His physical examination yielded no abnormalities, but it was found that he had 10 close relatives who had died during relatively minor surgeries because of an unknown cause. In the case reports that followed, a case fatality rate of 70% was mentioned and the link with halogenated volatile anesthetics and suxamethonium use was established. In the 1970s, the use of dantrolene in acute malignant hyperthermia helped reduce the mortality rate to 5–10% today [2].

Malignant hyperthermia is a hypermetabolic reaction caused by an excessive calcium release from the sarcoplasmic reticulum in skeletal muscles. This leads to energy depletion, rapid production of carbon dioxide and heat, offsetting a series of clinical events. The anesthesiologist might first notice a rise in end-tidal CO2, nonreactive to increasing ventilation, followed by tachycardia, tachypnea, hypotension, metabolic and respiratory acidosis, hyperkalemia, cardiac dysrhythmias, skeletal muscle rigidity and hyperthermia [2,3].

The prevalence of malignant hyperthermia is estimated at 1.5–2.5/100 000 general anesthesia events, even though the prevalence of malignant hyperthermia susceptibility is estimated at 1/2000 by the Malignant Hyperthermia Association of the United States [2,3]. This discrepancy is likely caused by incomplete penetrance and variable expressivity. In malignant hyperthermia susceptible individuals,

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KEY POINTS

- Mutations in the *RYR1*-gene are to date the most frequent genetic cause of malignant hyperthermia susceptibility.
- In spite of recent genetic advancements, the genetic basis of malignant hyperthermia is still not known in up to 50% of patients.
- A mutation in *RYR1* or a clinical *RYR1* phenotype does not automatically translate in malignant hyperthermia susceptibility, but precautions should be taken.
- Distinction between true malignant hyperthermia and malignant hyperthermia-like reactions is crucial, as not only the given preoperative advice differs, but also its acute treatment.

also physiological stressors such as severe exercise in hot conditions can trigger this reaction in the absence of halogenated anesthetics or depolarizing muscle relaxants such as succinylcholine. Malignant hyperthermia susceptibility is most often dominantly inherited. In up to 50% of malignant hyperthermia susceptible patients, mutations in the *RYR1*-gene, which encodes the skeletal muscle ryanodine receptor 1, are the most frequently identified genetic defects [4▪]. RYR1 regulates the movement of calcium from the sarcoplasmic reticulum into the intracellular space of the muscle cell. Less common, in 2% of the malignant hyperthermia susceptible individuals, mutations in the α-1 subunit of the dihydropyridine-sensitive L-type voltage-dependent calcium-channel receptor gene (*CACNA1S*) have been identified, and even more rarely in the SH3 and cysteine-rich domains 3 gene (*STAC3*). Both CACNA1S and STAC3 are also components of the (calcium dependent) excitation–contraction coupling machinery of skeletal muscles [4▪].

The scope of this review is to give an overview of neuromuscular disorders that can be linked with malignant hyperthermia or malignant hyperthermia-like reactions, and to suggest an appropriate approach to interpret the accompanying risks.

MYOPATHY PHENOTYPES ASSOCIATED WITH MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

Twenty years ago, an article published in the *Lancet* already discussed myopathies related with malignant hyperthermia susceptibility (MHS). Three were mentioned: central core disease, King–Denborough syndrome and 'Evans myopathy' [5]. The latter, named after the family in which malignant hyperthermia was first reported, was a descriptive term involving a variable phenotype, with or without muscle wasting, with aspecific myostructural changes on muscle biopsy and/or raised creatine kinase in serum. The three myopathies are linked through mutations in the same gene: *RYR1*. Today, we can add further diseases caused by mutations in *RYR1*, such as congenital myopathy with cores and rods, multiminicore myopathy and centronuclear myopathy.

Mutations in *CACNA1S* mainly cause hypokalemic periodic paralysis, but also a congenital myopathy, as well as rhabdomyolysis and asymptomatic hyperCKemia [6,7]. Mutations in *STAC3* cause Native American myopathy associated with malignant hyperthermia susceptibility, but likewise the spectrum of phenotypes has expanded recently, as the first non-Amerindian patient with Native American myopathy has been described, and *STAC3* mutations have also been reported in non-Native American patients with overlapping features of Carey–Fineman–Ziter syndrome and Moebius syndrome [8,9]. The phenotypes that have been shown to be associated with MHS are indicated in Table 1 [10–15,16▪,17,18].

It is important to note that a mutation in *RYR1* does not automatically mean that an individual is susceptible for malignant hyperthermia. Thus far, the 'European Malignant Hyperthermia Group' acknowledged 42 *RYR1* mutations (out of the 688 known variants) to be causative for MHS, as well as two *CACNA1S* mutations. Mutations in *RYR1* are the most common cause of congenital myopathies and can be inherited in an autosomal dominant or recessive manner. Mainly dominant mutations are linked to MHS, and it is estimated that only about 30% of patients with a proven *RYR1*-related myopathy phenotype are malignant hyperthermia susceptible [19]. However, until an in-vitro contracture test (IVCT) on muscle tissue has proven that a patient with an *RYR1*-related myopathy is not malignant hyperthermia susceptible, the patient should be treated as such. This also applies to family members of patients with a known *RYR1*-mutation.

Conversely, a (congenital) myopathy with a confirmed genetic diagnosis that is not a mutation in one of the three abovementioned genes can be regarded as nonrelated to malignant hyperthermia. Thus, most patients with a muscle disease will not be susceptible to malignant hyperthermia.

However, special care should be taken in patients with a personal or family history of a clinical malignant hyperthermia (-like) event caused by triggering anesthetics or certain physiological

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Table 1. Myopathies associated with malignant hyperthermia susceptibility

Myopathy	Gene, inheritance of myopathy	Evidence of association with MHS
Central core disease	*RYR1*, autosomal dominant with variable penetrance	Extensively established link with the *RYR1* genotype *in vitro* and *in vivo* [10,11]
King–Denborough syndrome	*RYR1*, autosomal dominant	Case reports linking some cases to *RYR1* mutations and MHS [12,13]
Congenital myopathy with cores and rods	*RYR1*, autosomal dominant	Case report of a triplet of *RYR1* variants in *cis* causing MHS; and the triplet in combination with a compound heterozygous *RYR1* mutation causing MHS and myopathy [14]
Multiminicore myopathy	*RYR1*, autosomal recessive or autosomal dominant	Case report linking a large autosomal dominant family with *RYR1* mutations and MHS [15]
Centronuclear myopathy	*RYR1*, autosomal recessive	Case report of a patient with an *RYR1* variant known to cause MHS (c.1201C>T; p.Arg401Cys); and the variant in combination with a compound heterozygous *RYR1* mutation causing MHS and myopathy [16▪]
Hypokalemic periodic paralysis	*CACNA1S*, autosomal dominant	Reports possibly linking *CACNA1S* mutation with MHS [17]
Native American myopathy	*STAC3*, autosomal recessive	Established link through case reports and pedigree studies [18]

stressors. A diagnostic pathway of malignant hyperthermia is summarized in Fig. 1.

OTHER 'NONMYOPATHY' PHENOTYPES ASSOCIATED WITH MALIGNANT HYPERTHERMIA SUSCEPTIBILITY

Malignant hyperthermia susceptibility is not limited to patients with myopathies. Indeed, most individuals who experience an malignant hyperthermia episode during anesthesia do not have a myopathy. Table 2 [20,21,22▪]indicates the nonmyopathy phenotypes of malignant hyperthermia susceptible patients: normal phenotype, idiopathic hyperCKemia and exertional rhabdomyolysis. Interestingly, in a recent study, a confirmed pathogenic *RYR1* mutation resulting in malignant hyperthermia susceptibility was found to cause

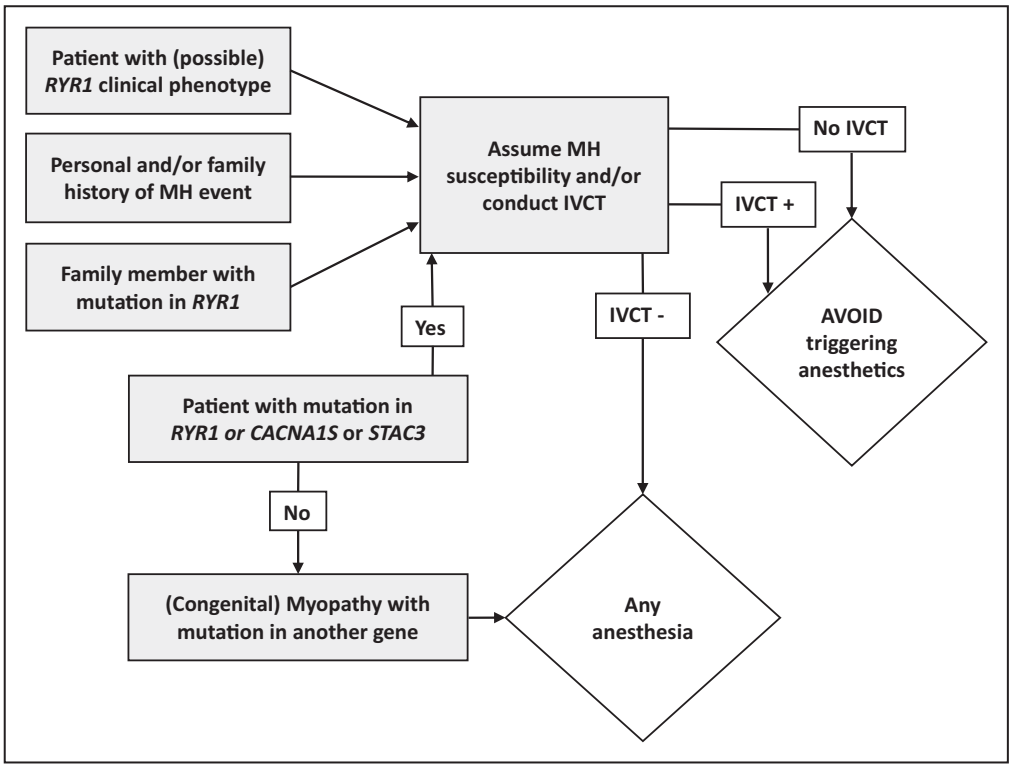

FIGURE 1. Diagnostic pathway of malignant hyperthermia. Schematic presentation of the diagnostic pathway of malignant hyperthermia. IVCT, in-vitro contracture test. For abbreviations of genes, see text.

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Table 2. Other 'nonmyopathy' phenotypes associated with malignant hyperthermia susceptibility

Phenotype	Genotype	Evidence
Normal	*RYR1* or *CACNA1S*, autosomal dominant	Confirmed in many healthy patients and families with clinical episodes of MH, including positive IVCT
Idiopathic hyperCKemia	With or without *RYR1* mutations	Positive IVCT in patients without *RYR1* mutations, and in one patient with *RYR1* mutations [20,21]
Exertional rhabdomyolysis	*RYR1* or *CACNA1S*	Positive IVCT in patients with exertional rhabdomyolysis and *RYR1* or *CACNA1S* mutations [22▪]

MH, malignant hyperthermia.

bleeding abnormalities in otherwise healthy individuals, further broadening the *RYR1* phenotypic spectrum [23].

The association between exertional rhabdomyolysis and MHS has been suggested a long time ago, but is at present still not fully elucidated. A recent Canadian case series and systematic review describes asymptomatic, predominantly muscular men who experienced rhabdomyolysis after a fairly standard physical exertion, sometimes combined with hot weather conditions or a concomitant viral illness. They provide multiple reports of positive IVCT and *RYR1* mutations in these patients, strongly arguing in favor of a connection [22▪]. However, several difficulties for interpretation of the data exist: both exertional rhabdomyolysis and MHS have a multifactorial cause, the majority of *RYR1* mutations identified are variants of unknown significance that have yet to be examined in segregation analyses and functional studies and *RYR1* mutations have a highly variable penetrance. Therefore, we conclude that a case-by-case approach is still warranted, as some patients with exertional rhabdomyolysis are most likely malignant hyperthermia susceptible (estimated at 20–30%), but most of them probably are not [22▪,24]. Furthermore, IVCT has only been validated in patients with a clinical suspected malignant hyperthermia episode and the sensitivity and specificity of this test is unknown in other settings, such as in patients with exertional rhabdomyolysis [25▪▪]. Patients with repeated muscle breakdown to physiological stressors, without a clear diagnosis, warrant special anesthetic considerations and should probably receive *RYR1* (and *CACNA1S*) genetic testing.

Idiopathic hyperCKemia has been linked to MHS in several studies. However, as idiopathic hyperCKemia is a nonspecific finding, related to a multitude of diseases, one could assume that it is but a marker for an underlying myopathy that is linked to MHS and thereby not itself related to malignant hyperthermia susceptibility.

NEUROMUSCULAR DISEASES ASSOCIATED WITH MALIGNANT HYPERTHERMIA-LIKE REACTIONS

Several neuromuscular diseases that were long presumed to be at increased risk of developing malignant hyperthermia are now known to be associated only with an malignant hyperthermia-like reaction in response to succinylcholine and possibly also halogenated anesthetics. One specific malignant hyperthermia-like reaction is anesthesia-induced rhabdomyolysis (AIR), which is a term that has been used since 1978 to describe a syndrome resembling malignant hyperthermia, but differing in cause and treatment. Although malignant hyperthermia is a hypermetabolic reaction that can finally lead to uncontrolled rhabdomyolysis, AIR presents with acute rhabdomyolysis and hyperkalemia leading to cardiac arrest, while the blood oxygen saturations are still within normal ranges. In contrast to malignant hyperthermia, AIR does not respond to dantrolene. The distinction between the two entities is crucial as the primary management is very different: in AIR, one should focus on reducing serum potassium and maintaining cardiac output, whereas in malignant hyperthermia initial treatment is providing dantrolene [26▪,27▪]. Neuromuscular diseases associated with malignant hyperthermia-like reactions are indicated in Table 3 [17,26▪,27▪,28–30].

Myotonic dystrophy type 1 (Steinert's disease) is an example of a neuromuscular disorder initially thought to be associated with malignant hyperthermia, but currently known to be at an equal risk for malignant hyperthermia in response to volatile anesthetics compared to the general population. However, in these patients, succinylcholine should still be avoided, because this muscle relaxant can provoke unpredictable muscle contractures and sometimes even an exaggerated hyperkalemic

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Table 3. Neuromuscular diseases associated with malignant hyperthermia-like reactions

Phenotype	Gene, inheritance	Evidence
Dystrophic and nondystrophic myotonias (except hypokalemic periodic paralysis, see Table 1)	Depends on the specific disease	Succinylcholine administration leads to a generalized skeletal muscle rigidity in myotonic dystrophy type 1 and 2, myotonia congenita, hyperkalemic periodic paralysis and to masseter spasm in paramyotonia congenita [17]
Duchenne and Becker muscular dystrophy	*DMD*, X-linked recessive	Well-established link with rhabdomyolysis and hyperkalemia in response to succinylcholine (and possibly volatile anesthetics), etiologically different from true MH [26▪,27▪]
Merosin-deficient congenital muscular dystrophy	*LAMA2*, autosomal recessive	One case report of an MH-like reaction in a patient who did not receive classic triggering anesthetics [28]
Carnitine palmitoyl transferase type 2 (CPT2) deficiency	*CPT2*, autosomal recessive	One case report of an MH-like reaction in CPT2-deficiency [29]
Guillain–Barré syndrome	–	Case reports of hyperkalemia leading to cardiac arrest after succinylcholine administration [30]

MH, malignant hyperthermia.

response [17]. Muscular dystrophies such as Duchenne and Becker muscular dystrophy can also be associated with an malignant hyperthermia-like reaction to succinylcholine [27▪].

There are little reports concerning the risk of malignant hyperthermia in patients with mitochondrial myopathies. In 1985, a letter was published, describing a successful treatment of malignant hyperthermia in a child with a mitochondrial myopathy who developed generalized muscle rigidity, hyperkalemia and a rise in temperature up to 38°C after administration of halothane and succinylcholine [31]. However, there is insufficient information to confirm that this was indeed a true malignant hyperthermia reaction or rather due to a cytoskeletal disruption effect of succinylcholine. Furthermore, a more recent study reported the safe use of volatile anesthetics in a large cohort of 107 patients with mitochondrial myopathies [32]. In contrast, a recent report described the possibility of coexistence of malignant hyperthermia susceptibility and mitochondrial disease in patients [33]. Currently, experts agree that care should be taken with the use of succinylcholine in patients with mitochondrial myopathy, but that no clear link with malignant hyperthermia is established.

In two autosomal recessive metabolic myopathies, myoadenylate deaminase deficiency and glycogen storage myopathy type 5 (McArdle disease), 10 and eight positive IVCTs have been obtained, respectively, however, without reports of clinical reactions in these patients, which renders the data inconclusive [34,35].

Several other neuromuscular diseases, such as Guillain–Barré syndrome (Table 3), chronic polyneuropathies, lower motor neuron disease and various causes of acute and progressive muscular atrophy, can also be accompanied with acute hyperkalemia after succinylcholine administration [27▪]. The proposed mechanism is a hypersensitivity of the muscle membrane because of an upregulation of acetylcholine receptors at the neuromuscular junction in response to long-term denervation. Diseases of the neuromuscular junction itself, such as myasthenia gravis and Lambert–Eaton myasthenic syndrome, do not, in fact, display malignant hyperthermia-like reactions in response to succinylcholine or volatile halogenated agents [27▪].

Finally, there are some rare syndromes, which are still often presumed to be associated with malignant hyperthermia susceptibility, even though this has been proven to be untrue. Examples include osteogenesis imperfecta, Noonan syndrome, arthrogryposis multiplex congenita, Schwartz–Jampel syndrome, Cornelia de Lange syndrome and neuroleptic malignant syndrome (which is typically confused because of its similar name) [35,36▪,37–39].

It is important to note that a positive IVCT cannot be interpreted unambiguously in the presence of a coexisting muscle disease. One can easily imagine that patients with 'membrane channelopathies', for example, are at an increased risk of having a false positive IVCT because of multiple confounding physiological variables, and it is therefore only warranted to assume malignant hyperthermia susceptibility if a clinical event has been observed in such patients. In the instance of mutations in the sodium voltage-gated channel α subunit 4 gene (*SCN4A*) causing periodic paralysis, associations with a positive IVCT have consequently led to the assumption that the patients are at an increased risk for malignant hyperthermia susceptibility [40]. However, the validity of an IVCT in these patients

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should be subjected to further studies before any such assumptions can be made.

RECENT FURTHER INTERESTING FINDINGS RELATED TO MALIGNANT HYPERTHERMIA

Two recent studies provide us with new insights in the mechanism of action of dantrolene, which has long been debated [41▪,42]. They showed that dantrolene increases the affinity of the ryanodine receptor to magnesium and that this – combined with a physiological increase in magnesium in malignant hyperthermia – leads to a depression of the overactive calcium release and resulting hypermetabolic reaction known as malignant hyperthermia.

In another recent study, the authors suggest that malignant hyperthermia susceptible patients might have an impaired aerobic metabolism, which would indeed offer a plausible explanation for the exercise intolerance of which they often complain [43].

It has long been known that elite athletes appear to be at a greater risk for severe malignant hyperthermia episodes. Indeed, a recent study demonstrated that male sex and muscular body build are both independently predictive of malignant hyperthermia susceptibility [44].

Interestingly, several studies have recently applied next-generation (whole)-exome sequencing and targeted gene panels comprising genes particularly involved in excitation–contraction coupling, in patients with MHS. They confirmed that up to 50% of malignant hyperthermia susceptible individuals do not carry pathogenic variants in known malignant hyperthermia genes. However, many variants of unknown significance in malignant hyperthermia genes were revealed. These state-of-the-art genetic studies have unfortunately not led to the discovery of many novel candidate genes. Rare variants in some additional genes (*CACNB1, CASQ1, SERCA1, CASQ2, KCNA1*) have been identified, but will remain variants of unknown significance until functional assays have proven their pathogenicity [45,46]. Furthermore, there are also plenty of variants of unknown significance in *RYR1* and *CACNA1S* that still need to be validated genetically and functionally [25▪▪,47▪,48,49].

CONCLUSION

We conclude that malignant hyperthermia is still highly relevant in neuromuscular disorders. Over the years, the phenotypes possibly linked to malignant hyperthermia have expanded, as have the number of pathogenic variants in known causative genes. However, in spite of recent genetic advancements, the genetic basis of malignant hyperthermia is not known in up to 50% of patients. This review provides a useful summary for the clinical practitioner to advise neuromuscular patients with regard to diagnostic testing and perioperative precautions.

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Conflicts of interest

There are no conflicts of interest.

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