Core Myopathies and Risk of Malignant Hyperthermia

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In this article, we analyze myopathies with cores, for which an association to malignant hyperthermia (MH) has been suggested. We discuss the clinical features, the underlying genetic defects, subsequent effects on cellular calcium metabolism, and *in vitro* muscle responses to MH triggers. We describe in detail central core disease, multiminicore disease, and nemaline rod myopathy. We categorize the diseases according to the affected proteins and discuss the risk for MH, which is high or theoretically possible when the calcium-conducting proteins are affected.
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Malignant hyperthermia (MH) is a pharmacogenetic disorder in which volatile anesthetics trigger a sustained release of Ca^{2+} from the sarcoplasmic reticulum that leads to hypermetabolism, muscle rigidity, rhabdomyolysis, and death. Although the mechanism of MH triggering is specific, the resulting clinical features are not. Thus, patients with a variety of neuromuscular disorders are sporadically reported to have developed one or more of the clinical features of MH (such as pyrexia, tachycardia, hypercapnia, and hyperkalemia) in the perioperative period. It is important to distinguish such nonspecific problems from MH, because the different underlying pathophysiological mechanism is likely to require different treatment and have different implications for future anesthetic management of the patient and their family. Therefore, except in conditions where sarcoplasmic reticulum Ca^{2+} release is specifically sensitized to volatile anesthetics, as in MH, these drugs should not be absolutely contraindicated. It will be apparent, therefore, that a fully informed decision concerning the use of volatile anesthetics in a patient with a myopathy requires an understanding of the underlying molecular defect. There are, however, other important factors that should be considered when planning anesthetic management in general, and choice of anesthetic drugs in particular, in patients with congenital myopathies and these will be briefly discussed before detailing specific myopathies.

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GENERAL CONSIDERATIONS WHEN ANESTHETIZING PATIENTS WITH CONGENITAL MYOPATHIES

Anesthetic management of patients with muscle diseases is challenging. In addition to unpredictable sporadic responses, such as rhabdomyolysis and metabolic stimulation, more predictable risks are associated with respiratory and bulbar muscle weakness, myocardial involvement, and difficult airway anatomy. To identify and minimize risk, a thorough preoperative workup is indispensable. Initially, a review of the diagnosis should be made in conjunction with the patient's neurologist. In the preoperative workup of a patient with a myopathy, the anesthesiologist should not be content with a diagnosis of a specific myopathy made purely on clinical features, but should try to establish the underlying molecular mechanism, i.e., the underlying mutated channel, for reasons that will become apparent later. Myopathies share common clinical features, and the underlying molecular mechanism is frequently not identified through clinical evaluation: histopathological examination of muscle biopsy specimens may be misleading, and optimal interpretation is a highly specialized field.

Confirmation of the diagnosis of the type of myopathy will determine further preoperative evaluation. Unlike the muscular dystrophies, the congenital myopathies are not usually associated with primary myocardial involvement, although scoliosis may be associated with a restrictive lung deficit, which in turn can lead to right ventricular strain and ultimately failure. Furthermore, skeletal muscle weakness can make it difficult to assess cardiovascular reserve from the history of daily activities.

The presence of skeletal muscle weakness itself, however, is a major concern for the anesthesiologist, especially if it involves the respiratory and/or bulbar

muscles. A formal clinical evaluation of respiratory and bulbar muscle function, appropriate to the age of the patient, is a mandatory aspect of the preoperative evaluation of patients with congenital myopathies. In older children and adults, this should be complemented by respiratory function tests. Sensitivity to respiratory-depressant drugs should be anticipated and, where possible, doses titrated to the desired effect. Even with the most careful anesthetic management, postoperative ventilatory support may be required and, therefore, postoperative intensive care unit availability should be planned. Furthermore, we consider it prudent to admit for overnight postoperative observation, rather than treat as a day case, any patient diagnosed preoperatively to have bulbar or respiratory muscle involvement even if they do not require immediate postoperative ventilatory support.

Our final recommended addition to routine preoperative management for patients with muscle diseases is baseline serum potassium and creatine kinase (CK) concentrations to assess muscle membrane integrity. It is possible that high baseline values may be associated with increased risk of profound perioperative rhabdomyolysis, whereas the baseline value *per se* is required to differentiate perioperative rhabdomyolysis from preexisting muscle damage.

All anesthetic techniques and drugs are associated with increased risk in patients with myopathies. Invariably, reducing the risk of one type of complication by avoiding a particular drug will lead to increasing the risk of another complication from the alternative drug. In such circumstances, a recommendation for an absolute contraindication to a drug in a particular patient group requires good evidence. Thus, because of the potential advantages of volatile anesthetics and potential disadvantages of alternative techniques, we consider it unhelpful to contraindicate their use in congenital myopathies except when the associated risk of MH is high for the myopathy under consideration.

The situation is different with succinylcholine. Use of depolarizing neuromuscular blocking drugs should be generally discouraged in patients with neuromuscular diseases. Although depolarizing muscle relaxants are triggers of MH, the prolonged depolarization leads to potassium release and calcium influx. These adverse effects are exaggerated in patients with extrajunctional acetylcholine receptors, increased proportion of the fetal γ-isoform, and those susceptible to myotonic reactions.[1] As the same might be true about reversal of neuromuscular block with anticholinesterases, this group of substances is generally not recommended in patients with neuromuscular diseases. The recent introduction of cyclodextrin reversal drugs (such as sugammadex) provides an attractive alternative in these circumstances. Succinylcholine may also cause acute profound rhabdomyolysis in patients susceptible to MH and those with one of a range of myopathies. If neuromuscular blockade is required, a nondepolarizing neuromuscular blocking drug should be used, albeit in the knowledge that patients with myopathies may show increased sensitivity to these drugs.

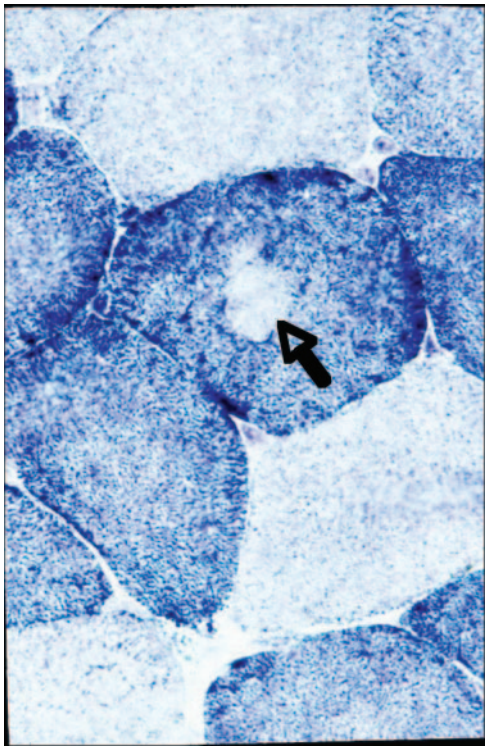

Figure 1. Histology of central core disease: muscle fibers containing unstructured cores (arrow) and no mitochondria (NADH reductase staining, ×400).

RYANODINE RECEPTOR GENE MUTATIONS AND MH

In up to 70% of MH families, variants in the skeletal muscle isoform of the ryanodine receptor (*RYR1*) gene have been identified.[2] Only 29 of the more than 200 sequence variations in *RYR1* have been investigated for their functional effect and meet the criteria to be included in the guidelines for molecular genetic detection of MH susceptibility (www.emhg.org). In the absence of a "high-throughput" method to investigate novel variants for their causativity, these functional analyses remain laborious, and they have not kept pace with the detection rate of novel variants in this large gene. Although it is likely that many of the currently uncharacterised *RYR1* variants associated with MH susceptibility will have pathological significance, until this is proven they have no diagnostic utility.[3] In these circumstances, patients with a personal or family history suggestive of MH should be considered at risk of the condition until proven otherwise by normal responses of muscle biopsy specimens to *in vitro* contracture tests (IVCT).

CENTRAL CORE DISEASE

Central core disease (CCD) is a rare hereditary myopathy, which presents clinically with muscle weakness of variable degree and histologically with central cores in the muscle fibers (Fig. 1). Common

features are floppy infant syndrome, delayed motor milestones, and generalized muscle hypotonia during adolescence. Additional features are skeletal abnormalities such as club foot, scoliosis, or hip displacement. There is no bulbar or diaphragmatic weakness and no external ophthalmoplegia. In adulthood, the syndrome usually is nonprogressive. Functional improvement can occur and approximately 40% of affected adults are considered asymptomatic. However, the evolution is unpredictable, and weakness may cause severe disability in daily life.[4,5]

Laboratory investigations reveal serum CK concentrations that are normal or slightly elevated. Histological findings are characterized by demarcated cores, which lack oxidative enzyme activity. The cores are only found in the predominant Type I fibers. The muscle involvement can also be demonstrated by various imaging techniques.[6]

Genetic Basis of CCD

The mode of inheritance of CCD is autosomal dominant. Disease-causing mutations in, or linkage to, *RYR1* have been shown in the majority of cases. Recessive transmission has been described for variant forms of CCD.[7] There is also an overlap of CCD with other myopathies (e.g., nemaline myopathy [NM] and multiminicore disease [MmD]).[8]

CCD and MH-Susceptibility

The clinical severity of CCD and the number of cores can vary with age: there is also variability between and within families. Individuals with MH susceptibility may have cores in the muscle but the diagnosis of CCD should be limited to those with a clinical myopathy. The current understanding of CCD suggests a strong link between subcellular Ca^{2+} metabolism and the pathophysiological mechanism of the disease.[2,9] This is corroborated by clinical episodes of MH and pathological contractures in the MH-diagnostic IVCT in some patients with CCD. However, in some cases of patients tested for MH susceptibility because of a diagnosis of CCD, rather than a suspected clinical MH episode, the IVCT gives negative results.[10,11] These findings are consistent with evidence that some CCD mutations in the C-terminal region of the RyR1 protein are associated with excitation-contraction uncoupling or a partially depleted sarcoplasmic reticulum through a constant Ca^{2+} leak (Fig. 2).[12] The resulting myoplasmic Ca^{2+} overload has been associated with mitochondrial damage.[13] On the other hand, both mechanisms lead to lower peak Ca^{2+} levels, which explains the muscle weakness and the lower *in vitro* sensitivity to Ca^{2+}-releasing drugs.[14,15] However, there are insufficient genotype-phenotype correlations, to make a definitive statement about the clinical risk, based on mutation type alone, and caution persuades us to recommend a non-triggering anesthetic unless the patient has had a normal IVCT.

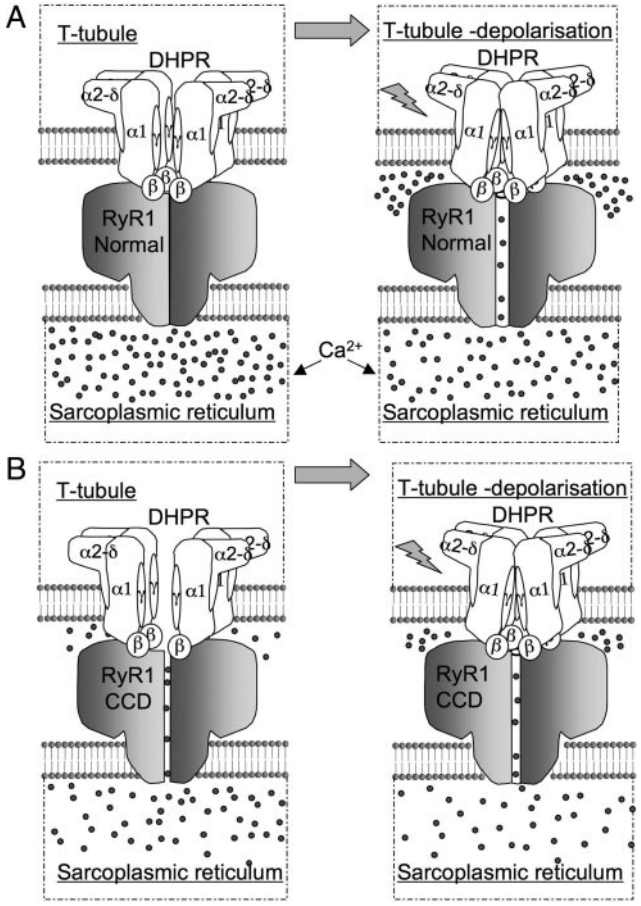

Figure 2. Cartoon of the key structures of excitation contraction coupling (EC-coupling) in the transverse tubule (T-tubule) of skeletal muscle. The dihydropyridine receptor (DHPR) is linked to the homotetrameric ryanodine receptor (RyR), which is the calcium release channel situated in the membrane of the sarcoplasmic reticulum (SR). The cytosolic part of the protein complex, the so-called foot, bridges the gap between the T-tubular system and the SR. Normally (A), the RyR channel is active only when the DHPR responds to T-tubule depolarization. In B, a leaky RyR channel and impaired EC-coupling due to C-terminal RYR1 mutations lead to central core disease (CCD).

MULTIMINICORE DISEASE

MmD is usually considered a recessively inherited congenital myopathy with a pattern of weakness that differs from CCD in that there is often severe axial involvement, while respiratory, bulbar, and extraocular muscles are commonly affected. As with CCD, the condition is stable or minimally progressive and the serum CK normal or only mildly elevated. MmD is characterized by cores lacking oxidative enzyme activity on histochemical analysis. However, in contrast to CCD, the cores in MmD are usually multiple, poorly defined (Fig. 3), and do not extend along the axis of the fiber. Four clinical subtypes of MmD have been described[16]:

1. The classical form, which is the most prevalent, consists of axial muscle weakness, commonly leading to severe scoliosis.
2. The moderate form with hand involvement, consists of generalized muscle weakness affecting

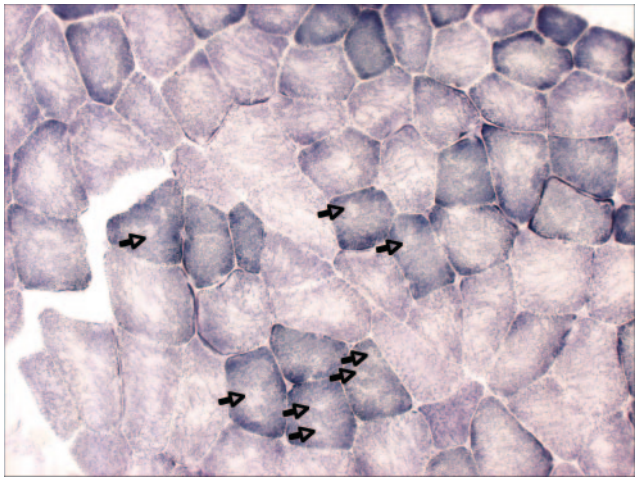

Figure 3. Histology of multiminicore disease. Oxidative enzyme staining (NADH, ×200) reveals multiple, poorly-defined cores (some cores are highlighted by arrows). Image provided by Professor Francesco Muntoni, Institute of Child Health, London, UK.

predominantly the pelvic girdle but also includes amyotrophy and hyperlaxity: in this form scoliosis is mild or absent.
3. A form that is similar to classical MmD but also includes ophthalmoplegia.
4. Antenatal onset MmD with arthrogryposis (multiple joint contractures).

Genetic Basis of MmD

MmD is genetically heterogeneous. The moderate form with hand involvement is most often associated with mutations in *RYR1*.[17] These can be homozygous, compound heterozygous, or heterozygous with monoallelic expression.[17–19] At least 10 different *RYR1* variants have been associated with cases of MmD, and these variants are spread across the *RYR1* gene.[2]

The classical predominant form of MmD is, however, most frequently associated with mutations in the selenoprotein N 1 gene.[20] This is the same gene that is responsible for congenital muscular dystrophy with rigid spine.[21] Selenoprotein has recently been shown to be required for RyR1 calcium release.[22] Mutations in patients with core myopathies have also been described in the α-actin gene (*ACTA1*).[23] Furthermore, there are myopathic patients with histological cores in whom mutations in *RYR1*, *ACTA1*, and selenoprotein N 1 gene have been excluded.

MmD and MH Susceptibility

There are no reports of patients with MmD developing clinical MH during general anesthesia: indeed, we could find no reports of potent inhaled anesthetics being used in a patient with MmD. Therefore, there are no reports of conventional MH diagnostic tests done on muscle biopsy specimens from patients with MmD, although abnormal Ca^{2+} release has been reported in a skinned fiber preparation from a Japanese patient with MmD.[24] The functional effects of MmD-associated *RYR1* mutations have been studied in HEK293 cells and in immortalized lymphocytes[25]: some of these mutations result in increased evoked Ca^{2+} release whereas others do not.

There is, however, a report of a large MH kindred in whom the majority of MH susceptible individuals have histopathological features of MmD but have no clinical myopathy.[26] There also seems to be a growing recognition that there is considerable overlap between CCD and MmD. In some patients with clinical features more consistent with CCD, histology reveals multiple cores or minicores. Indeed, a time-related change in the morphology from minicores to cores has been described.[27] So, although there is no definitive evidence to absolutely contraindicate volatile anesthetics in MmD, we would currently advise caution in patients with MmD with a *RYR1* etiology. It may indeed be a pragmatic approach, at least in respect to the association of core myopathies with MH, to consider the possibility of MH risk to be associated with an *RYR1,* rather than a core histology, etiology.

NEMALINE ROD MYOPATHY

NM is a rare congenital myopathy with an incidence of about two cases per 100,000 live births.[28] NM has considerable clinical and genetic heterogeneity.[28–30] The cardinal features of all nemaline subtypes are muscle weakness and the presence of nemaline bodies (rod-shaped structures) in the muscle fibers.[31,32]

Phenotype

The clinical spectrum of NM ranges from a severe fatal neonatal form to adult onset forms. The European Neuromuscular Centre International Consortium report on NM classifies the disease into six different subtypes: 1) severe congenital; 2) intermediate congenital; 3) typical congenital; 4) mild childhood; 5) adult onset; and 6) other forms.[33] NM is typically mild, nonprogressive, or slowly progressive with hypotonia and feeding difficulties in early life, small muscles, slender extremities, and proximal muscle weakness. The latter may also appear in the distal limb, neck flexor, trunk muscles, and in facial and masticatory muscles. Dysmorphic features include narrow, high-arched palate, micrognathia or marked prognathism, chest deformities, contractures of the fingers, and pes cavus or talipes equinovarus. A murine model of NM has been established, but the association of MH with NM has not yet been studied in this model.[34]

Histology

NM is characterized by dense sarcoplasmic inclusions in extrafusal skeletal muscle fibers[32] (Fig. 4). These rod bodies are assembled in an irregular distribution as clusters. They are derived from the Z-disk and consist of Z-disk proteins (α-actinin and actin).[35] In the vast majority of cases, the inclusions are located exclusively in the cytoplasm, about 10% of patients

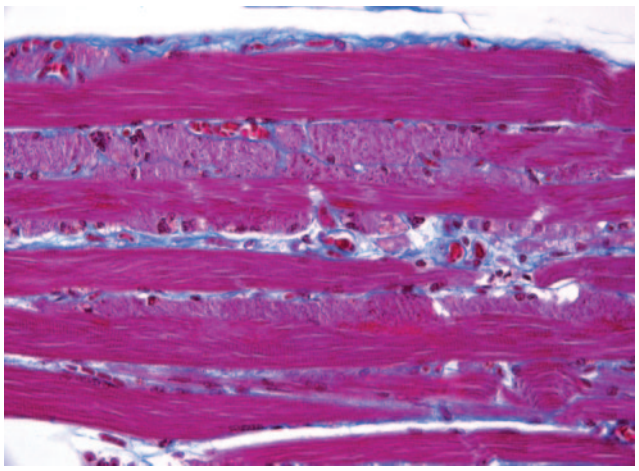

Figure 4. Skeletal muscle of an adult nemaline myopathy, autopsy case. In the longitudinal section of several muscle fibers shown here, the normal cross-striated fibrils are partially replaced by accumulations of rod-shaped nemaline bodies (Masson, ×400).

Table 1. Core Myopathies and Genes Associated with the Diseases and Estimated Risk of MH (Given There Is No Particular Malignant Hypothermia (MH) History in Family)

Disease	Gene	MH risk
Central core disease (CCD)	*RYR1*	High[a]
Multiminicore disease	*SEPN1*	Low
	ACTA1	Low
	RYR1	High[a]
Nemaline rod myopathy	*NEB, TPM3, TNNT1, TPM2, ACTA1*	Low
	RYR1	High[a]

The table summarizes molecular genetic knowledge, i.e., involved genes, of the different core myopathies. Emphasis should be on the underlying molecular pathology rather than phenotypic presentation. In patients in whom the genes associated with MH (*RYR1* and the α-1 subunit of the dihydropyridine receptor, *CACNA1S*) are involved, a nontriggering anesthesia technique is to be chosen. Websites of the North American and the European MH Group provide further information available at: www.mhaus.org and www.emhg.org.

RYR1 = ryanodine receptor Type 1; *SEPN1* = selenoprotein N1; *ACTA1* = α-actine; *NEB* = nebuline; *TPM3* = tropomyosin 3; *TNNT1* = troponin T1; *TPM2* = β-tropomyosin.

[a] Dependent on the underlying mutation; to be on the safe side, risk to be considered high until more information becomes available.

with NM also show intranuclear deposits.[36,37] Rare intranuclear inclusions appear to be associated with a more rapid progression and a worse outcome.

It has been hypothesized that the hypotonia may be caused by an altered regulation of Ca^{2+} activated force production in the muscle fibers and that rod formation is secondary to contractile dysfunction.[38,39]

Genetic Basis of NM

Most cases of NM are sporadic (approximately 63%). Familial forms are observed in about one-third of cases (24% autosomal recessive and 13% autosomal dominant).[30] Five genes have been associated with NM, all encoding known components of skeletal muscle sarcomeric thin filaments: 1) slow α-tropomyosin 3 gene[40]; 2) slow troponin T1 gene[41]; 3) β-tropomyosin gene[42]; 4) nebulin gene[43]; and 5) *ACTA1*.[44,45] In many cases, there is no strict genotype-phenotype correlation, indicating clinical and genetic heterogeneity of the disease.[46]

In the majority of cases, NM is caused by mutations in the nebulin gene,[47] in particular by dominant *de novo* mutations, followed by mutations in the *ACTA1* gene.[48] In a few cases, mutations in *RYR1* have also been associated with nemaline bodies. However, these nemaline bodies appeared together with central cores, indicating a mixed core-rod myopathy.[49–51]

NM and MH Susceptibility

There are few reports concerning the anesthetic implications of NM, but they focus on the management of patients with NM with poor respiratory function (muscle weakness and thoracic deformities) or difficulties with orotracheal intubation (in case of facial dysmorphism).[52–54] Concerns about the association of NM with MH appear to be of secondary relevance. As in other neuromuscular disorders, the use of depolarizing muscle relaxants is generally not recommended in patients with NM to avoid the potential risk of developing muscle damage or life-threatening hyperkalemia as well as other nonspecific symptoms.[55,56] A close association between typical NM (patients who exclusively present rod bodies) and MH is rather unlikely, because there are no reports in which patients with NM developed a severe MH crisis or were tested as MH susceptible by IVCT.

Some patients exhibit the histological feature of cores and rods in the same muscle biopsy. Based on reports in the literature, it may be hypothesized that in these patients' nemaline (like) bodies may be a secondary feature of CCD and that the CCD itself may represent the major risk factor for MH reactions.[49,51,57] There are insufficient data to draw a firm conclusion but for reasons of patient safety, we suggest managing these patients as we describe for patients with CCD.

CONCLUSION

There is definitive clinical and laboratory evidence that some *RYR1* mutations are associated with the coexistence of MH and CCD phenotypes: MH triggering drugs are contraindicated in patients with CCD carrying these mutations. There is less certainty about the MH risk for patients with CCD or other congenital myopathies who carry other *RYR1* mutations. In congenital myopathies caused by mutations in genes other than *RYR1*, the risk of MH appears to be low. Table 1 in this article gives a summary of the genes involved in the covered diseases and aims at estimating the associated risk of MH.

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