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REVIEW ARTICLE

Core myopathies and malignant hyperthermia susceptibility: a review

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Summary

The core myopathies are a subset of myopathies that present in infancy with hypotonia and muscle weakness. They were formerly considered a rare type of congenital myopathy but are now recognized as being more prevalent. Due to their genetic linkage to mutations in the ryanodine receptor gene (*RYR1*), core myopathies (in particular, central core disease) carry a high risk of malignant hyperthermia susceptibility. In this review article, we describe the phenotypical, genetic, and histopathological characteristics of core myopathies and further describe the currently understood nature of their risk of malignant hyperthermia. We also review the level of suspicion a clinician should exhibit with a child who has a possible core myopathy or other congenital myopathy presenting for an anesthetic prior to a definitive genetic analysis. For this review article, we performed literature searches using the key words anesthesiology, core myopathies, pediatric neurology, malignant hyperthermia, genetics, ryanodine receptor, and molecular biology. We also relied on literature accumulated by the two authors, who served as hotline consultants for the Malignant Hyperthermia Hotline of the Malignant Hyperthermia Association of the United States (MHAUS) for the past 12 years.

Core myopathies: general description

Core myopathies are the most common of the congenital myopathies (1). They are genetically heterogeneous with a common histopathological identity of focally reduced oxidative enzyme activity, called cores, either centrally or eccentrically located within the muscle cell (2–4). Clinically, core myopathies present with hypotonia and weakness from birth, or, less commonly, they present in later ages: older children or even adults. There is no definitive treatment for the core myopathies; treatment consists of physical and occupational therapies and nutritional support. Diagnosis of a core myopathy may be challenging and requires clinical presentation, histopathological evidence, genetic analysis, and, more recently, muscle magnetic resonance imaging (MRI) revealing the selective involvement of certain muscles (5,6). Much more is now known about the potential genetic causes of core myopathies. The most common mutation identified in the core myopathies is in the *RYR1* gene coding for the ryanodine receptor (2,7). Mutations in the *RYR1* gene also result in malignant hyperthermia susceptibility (MHS), and a risk of MHS has been shown in patients with core myopathy (8,9). This review will discuss the recent developments in the characterization of the different core myopathies with the advances in genotype/phenotype differentiation. We will discuss the potential coexistent risks of the various core myopathies and their MHS trait relative to the locations of mutations along the *RYR1* gene. In addition, we will discuss the implications of cores being noted in other congenital myopathies and their possible implications for MHS.

Central core disease

Central core disease (CCD) is a congenital myopathy presenting with muscle weakness and defined by the presence

of central cores, which are areas of reduced oxidative activity extending along the entire length of the muscle fiber on muscle biopsy (3,10). Central core disease was first described by Magee and Shy (11). The usual clinical presentation of patients with CCD is hypotonia and motor delays in infancy. The clinical spectrum of CCD may be broad and could range from akinesia in fetal life to muscle weakness in adults. When onset is in adult life, axial muscle weakness is typically most prominent (12). Congenital dislocation of the hips, scoliosis, foot deformities, and ligamentous laxity with patellar instability have been observed in patients with CCD. Cardiomyopathy and ophthalmoplegia are not typical features of CCD. The clinical progression of the disease may be static or slowly progressive. Serum creatine kinase levels are usually normal, even though mild elevation may be seen (13). The recent use of muscle MRI in patients with CCD has delineated more clearly the typical selective muscle involvement, with predilection for vasti muscles, sartorius and adductor magnus within the thigh, and the soleus muscle and peroneal group within the lower leg. In most patients, rectus femoris, adductor longus, and gracilis muscles are selectively spared (5,6,14).

Central core disease inheritance is primarily autosomal dominant with *RYR1* missense mutations (8,15). Recessive inheritance patterns have been reported where the parents of the affected patients were clinically unaffected but were heterozygous for the presence of *RYR1* mutation (16). The *RYR1* mutations are described as typically located in one of the three 'hot spot' regions on the protein: N-terminal, central, and C-terminal. They are also referred to as domains 1–3, respectively (17,18). Domain 3, which is located in the C-terminus of the protein and is the pore-forming region of the protein channel, has been the site of most CCD mutations (8,9,17,19,20); though, evidence is accumulating of CCD mutations located outside of domain 3 (2).

Multiminicore disease

Multiminicore disease (MmD) was first described by Engel *et al*. (21). Histopathologically, it has multiple focal areas of reduced oxidative activity in muscle fibers, which, in contrast to CCD, do not extend the entire length of the muscle fiber (7). Clinical presentation in MmD is more variable than in CCD (3,22,23). Traditionally, MmD has been divided into four major groupings: (i) classic form; (ii) moderate form with hand involvement; (iii) antenatal form with arthrogryposis multiplex congenita; and (iv) ophthalmoplegic form (3). It is now recognized that there is substantial overlap between the latter three forms because of a shared genetic background.

In contrast to the above grouping, the clinical presentations are more recently grouped according to the genotype, (24) which shows a recessive inheritance pattern either involving the selenoprotein N gene (*SEPN1*) on chromosome 1p36 or the *RYR1* gene on chromosome 19q13.2 (25–27). Selenoprotein N is involved in both antioxidant functions and calcium homeostasis, possibly by close association with *RYR1* (28,29). Mutations in the *SEPN1* gene are responsible for the traditionally categorized classic form of MmD. The classic form presents at birth with hypotonia, delayed motor milestones, and failure to thrive. Muscle weakness involves both axial and proximal muscles, notably in the shoulder girdle, accompanied by spinal rigidity and progressive scoliosis with resultant restrictive lung disease (3,7,30).

Multiminicore disease caused by recessive *RYR1* mutations presents with proximal muscle weakness similar in distribution to CCD, especially in the hip girdle, as opposed to the shoulder girdle weakness seen in MmD due to mutation in *SEPN1*. *RYR1* MmD also frequently exhibits distal muscle weakness with hand involvement. Exertional myalgias are common. External ophthalmoplegia is characteristic of some *RYR1*-related MmD phenotypes (16,24), but it is not typically seen in *SEPN1*-related MmD (7).

Primary cardiomyopathy is not found in *RYR1* or *SEPN1* MmD. Secondary cardiac involvement due to restrictive lung disease in MmD patients with severe scoliosis and spinal rigidity may result and has been described in *SEPN1* MmD (4,7). Primary cardiomyopathies are found with mutations in alpha-actin (*ACTA1*), beta-myosin heavy chain (*MYH7*), lamin A/C (*LMNA*), and the giant titin (*TTN*) genes associated with muscle filaments and proteins (31).

Recessive *RYR1* mutations in MmD are distributed throughout the *RYR1* genome as opposed to the three hot spots described in MHS/CCD or CCD (16,27). In contrast to leaky calcium channels or excitation–contraction (E-C) uncoupling seen in CCD with dominant *RYR1* causative mutations, muscle weakness in MmD is thought to be due to loss of calcium conductance through the ryanodine receptor from *RYR1* protein reduction (22,26). In some recessive *RYR1* mutations, there is evidence of a histopathological continuum between minicores and central cores over time (25,32).

Histological appearance of minicores may differ based on the mutation involved. *SEPN1* minicores are smaller, less defined, and more scattered than *RYR1* minicores. There is less predominance and uniformity of type 1 fiber involvement in MmD compared to CCD. Muscle MRI can reveal selective muscle involvement in MmD as is seen in CCD (2,4,25) but is usually more diffuse (6). Patients with MmD who carry *RYR1* mutations

are considered malignant hyperthermia (MH) susceptible; because the recessive *RYR1* mutations associated with MmD have not been functionally characterized yet, the precise MH risk associated with these mutations remains currently uncertain. There have been reports of MmD patients with recessive *RYR1* mutations with MH episodes but no reported cases of MH in MmD patients with *SEPN1* mutations (3).

Other congenital myopathies with cores or *RYR1* variants

Nemaline myopathy is a genetically heterogeneous congenital myopathy involving defects in skeletal muscle thin filaments (33). The classic histopathological marker is the rod body in muscle biopsy, composed of alpha-actinin and actin resulting from breakdown of the Z-discs in the sarcomere. Genetic mutations in nemaline myopathy involve genes encoding for skeletal muscle thin filament proteins, such as nebulin (*NEB*), *ACTA1*, beta-tropomyosin (*TPM2*), slow alpha-tropomyosin (*TPM3*), slow skeletal muscle troponin-T (*TNNT1*), and cofilin-2 (*CFL2*) (2,34). Mutations in *RYR1* have not been identified in nemaline myopathy; however, cores and rods have been described in biopsy specimens from both *RYR1* and *NEB* myopathies (35,36). Patients with nemaline myopathy are not considered MH susceptible, but patients with core-rod myopathy with an *RYR1* variant would be considered MH susceptible.

Centronuclear myopathy (CNM) is another genetically heterogeneous congenital myopathy with the histopathological characteristic of centrally placed nuclei in muscle fibers. The inheritance may be autosomal dominant, autosomal recessive, or X-linked. Mutations have been located in the dynamin 2 (*DNM2*), myotubularin (*MTM1*), amphiphysin 2 (*BIN1*), and *RYR1* genes (26,37–39). Although not considered a core myopathy, there have been reports of patients with *RYR1* centronuclear myopathy exhibiting cores on muscle biopsy at older ages (40,41). Patients with centronuclear myopathy who carry *RYR1* variants are considered MH susceptible.

Congenital fiber type disproportion (CFTD) is another congenital myopathy associated with *RYR1* mutations, as well as mutations in *SEPN1*, *ACTA1*, and tropomyosin 3 (*TPM3*). Muscle biopsy findings are characterized by small type 1 fibers with no evidence of cores, rods, or central nuclei (42,43). MHS should be considered a possibility in patients with *RYR1* variant-related CFTD (44).

King–Denborough syndrome is a myopathic syndrome comprising hypotonia, delayed motor milestones, proximal weakness, joint hypermobility, scoliosis, lumbar lordosis, scapular winging, and pectus excavatum; craniofacial features include micrognathia, high-arched palate, epicanthic folds, down-slanting palpebral fissures, hypertelorism, low set ears, malar hypoplasia, and ptosis. *RYR1* mutations are reported in King–Denborough syndrome. Although not a consistent histopathological feature, cores may be seen in some patients with King–Denborough syndrome (45). Patients with King–Denborough syndrome are considered MHS (46–48).

Malignant hyperthermia susceptibility trait

Malignant hyperthermia susceptibility trait is a pharmacogenetic disorder of skeletal muscle that can lead to a hypermetabolic response when exposed to a provocative environment, such as anesthetic agents (namely, volatile anesthetics and the depolarizing muscle relaxant succinylcholine). Rarely, MH may occur in a nonanesthetized patient (referred to as 'awake MH') as described in a recent report of a six-year-old boy who developed fulminant MH while playing outside. Histological and genetic postmortem studies revealed that the child had CCD and carried a novel variant on *RYR1*. Further studies of the family members revealed that the father and the two siblings have the same *RYR1* variant. The father, in addition to having histological evidence of CCD, demonstrated a strong positive reaction to the caffeine–halothane contracture test (49).

There is sufficient evidence to consider MH susceptibility as a subclinical myopathy despite the lack of phenotypical expression prior to exposure to a triggering environment. Upon exposure to such a triggering environment, patients with MHS may quickly and explosively develop a picture consistent with severe myopathy and rhabdomyolysis. The molecular pathophysiology of MH is defective intracellular calcium homeostasis upon exposure to a triggering agent, resulting in a massive and unregulated rise in myoplasmic calcium with a phenotypical behavior often seen as sustained muscle rigidity and hypermetabolism. The disease manifests clinically as a significant rise in ETCO2 (which cannot be controlled by increases in minute ventilation), tachycardia, muscle rigidity, and temperature elevation (50–52). The sustained muscle contraction and hypermetabolism cause depletion of ATP with cellular anoxia (53), resulting in disruption of the muscle cell membrane integrity and leading to rhabdomyolysis and hyperkalemia. Unless aborted promptly, MH is fatal, due to the end organ failure, including the most commonly observed complications: hyperkalemic cardiac arrest, acute renal failure, and disseminated intravascular coagulopathy (52,54). Treating an MH episode consists of immediately ceasing triggering agents, administering dantrolene, cooling the patient, and treating complications.

Incidence rate of MH varies between countries (55), and precise determination is difficult. A recent study examining discharge data from all hospitals in New York (n = 12.7 million records) for years 2001 to 2005 estimated the MH incidence rate as 0.96 per 100,000 surgical cases (56). This study observed a higher MH incidence rate (2.5–4.5 times) in males compared to females, similar to findings from another study that examined the database maintained by the United States Malignant Hyperthermia Registry (54). The morbidity from MH has declined since the introduction of dantrolene but remains as high as 35%, reported in the 2010 study (54) examining data from the North American registry.

RYR1: Genetic link associating core myopathies and MHS

The link between core myopathies and MHS is the *RYR1* gene that codes the ryanodine receptor, which is a large ion channel that facilitates calcium release from the sarcoplasmic reticulum during E-C coupling (57). The ryanodine receptor is a homotetrameric protein that, upon sarcolemmal depolarization, interacts with the L-type voltage-gated calcium channels known as dihydropyridine receptors (DHPR). Opening of the ryanodine receptor releases calcium from the sarcoplasmic reticulum into the myoplasm, allowing the initiation of myofilament cross-linking and, thus, muscle contraction. Mutations in *RYR1* are the most common cause of MHS trait, which is a heterogeneous disease with an autosomal dominant inheritance (58). The *RYR1* gene on chromosome 19q13.1 was linked to human MH (59,60) in 1990, followed by the linkage of *RYR1* mutations and CCD (61,62) in 1993. The terminology 'mutation versus variant' in *RYR1* gene is likely to cause misunderstanding among clinical practitioners who otherwise are not closely associated with genetics. Mutations are variants functionally characterized using recognized standards and when positive are considered causative of MH (63). Over 300 *RYR1 variants* have been identified (64), and to date, only 31 *RYR1* mutations have been functionally tested as MH causative according to the European MH Group (EMHG) guidelines (65) at the MH Investigation Unit at St James's Hospital, Leeds, UK. With many more *RYR1* variants requiring functional analysis before being labeled as MH causative, more mutations undoubtedly will continue to be discovered, both in the *RYR1* gene and in other loci. With the current genetic testing offered to MHS patients, approximately 30% are found to carry a causative *RYR1* mutation. A second gene, a voltage-dependent, L-type calcium channel, alpha 1S subunit (*CACNA1S*), which codes for one of the subunits of the skeletal muscle DHPR at locus 1q32, is also under investigation in MH susceptibility. To date, three variants have been found in the *CACNA1S* gene in MHS patients (66–71). These have not been functionally characterized as MH causative by EMHG criteria, nor have any *CACNA1S* variants been implicated in core myopathy.

The pathophysiology of the mutated *RYR1* is thought to involve four mechanisms, which may begin to elucidate both the calcium dysregulation and hypermetabolism of MH and the muscle weakness of CCD and MmD. The four mechanisms are as follows: (i) a hyper-responsive ryanodine receptor in MHS responsible for calcium dysregulation in skeletal muscle cells leading to the phenotypical presentation of MH; (ii) a 'leaky' ryanodine receptor in CCD, potentially causing skeletal muscle weakness; (iii) E-C uncoupling in CCD also causing skeletal muscle weakness; and (iv) overall loss of *RYR1* protein in recessive *RYR1* mutations, leading to *RYR1* dysfunction and skeletal muscle weakness (19,72,73). Research is ongoing in attempts to clarify and expand on these postulated pathophysiological mechanisms.

Historically, the swine model was invaluable in gaining understanding of the pathophysiology of triggering MH and the early identification of mutated *RYR1* as a cause of MH. The *RyR1* mutation leading to MHS in swine has a recessive pattern, while a dominant pattern is predominantly seen in humans. More recently, a knock-in mouse model heterozygous for *RyR1* (Y522S) has been developed, which has shown great potential as a model for human MH pathophysiology and also as a model for studying the temporal development of core formation in skeletal muscle (32,74,75).

Anesthetic and clinical dilemmas

Both core myopathies and MHS are heterogeneous diseases and are further complicated by their complex genotype–phenotype presentations. Determining whether an *RYR1* variant is causative for CCD, MmD, or MHS is laborious. The histopathological markers in muscle biopsy specimens–namely cores, rods, centralized nuclei, and type 1 fiber predominance–have been found across the spectrum of the different congenital myopathies. Rods and central nuclei have been seen in some patients with core myopathy, and cores have been found in patients with CNM and in patients with MHS (2,15). Cores are also found after eccentric muscle exercise, after surgical tenotomy or trauma, and in patients with MHS but no clinical presentation of muscle weakness (3). The neurology community does not consider cores on muscle biopsy without clinical myopathy evidence enough to classify a patient as having a core myopathy (3,23).

Designing an anesthetic for a patient with a known or suspected diagnosis of core myopathy

Designing an anesthetic plan for patients with a core myopathy is difficult because of the profound genotype–phenotype variability that makes a definitive diagnosis prior to the anesthetic challenging. If the diagnosis is not already known, the most information the anesthesiologist may have is a clinical presentation suspicious of a congenital myopathy, core myopathy being just one subgroup among them. Children often present for orthopedic procedures such as clubfoot or congenital hip dislocation before a diagnosis is made. These children may also present for anesthesia for medical imaging studies or muscle biopsies as part of their diagnostic workup for hypotonia and motor delays. In children with clinical features of a core myopathy but a history of a normal muscle biopsy, the diagnosis of core myopathy is not excluded because cores may not develop until the child is older (2).

Cores also have a predilection for certain muscle groups, and therefore, the location of the muscle biopsy is important (3). Moreover, it is not the presence of cores in muscles that heralds MHS but rather the presence of an *RYR1* MH causative mutation. The dilemma is in identifying the subgroups of core myopathy patients (or congenital myopathy patients in general) that have *RYR1* variants, as children often present for procedures requiring anesthesia prior to any genetic workup, and *RYR1*-specific genetic analysis is not typically part of the workup in such situations (see Table 1).

For children presenting for an anesthetic and suspected to have a congenital core myopathy, the anesthesiologist needs to carefully review the clinical history and any available diagnostic information, such as histopathology from muscle biopsy, metabolic workup (including creatine phosphokinase [CPK] measurements), and any genetic analysis, if performed. All of the clinical and diagnostic information should be discussed with the child's neurologist to determine which type of congenital myopathy is most likely present in the patient.

If the clinical picture is consistent with a possible core myopathy or other congenital myopathy associated with *RYR1* mutations, the anesthetic should be designed with MHS in mind. As with any anesthetic, careful monitoring of all vital signs, including ETCO2 and core temperature, is essential. Additional monitoring of CPK levels, K+, and urine output and color may be warranted. A thoughtfully designed anesthetic approach based on review of the clinical information and discussion with the neurology consultant is preferred over a generalized approach of

Table 1 Main clinical and histopathological features in core myopathies due to mutations in the skeletal muscle ryanodine receptor (*RYR1*) and the selenoprotein N (*SEPN1*) genes and genetically distinct congenital myopathies (3)

Gene	*RYR1* ad	*RYR1* ar	*SEPN1*	*MTM1*	*DNM2*	*NEB*	*ACTA1*
Frequency	+++	+++	++	++	+	++	++
Onset							
Infancy	++	+++	++	+++	+	+++	++
Childhood	+++	++	+++	+	+	+	++
Adolescence/adulthood	+	+	–	–	++	–	–
Clinical features							
External ophthalmoplegia	+	+++	–	+++	+++	–	–
Bulbar involvement	+	+++	++	+++	++	+++	++
Respiratory involvement	+	++	+++	+++	++	++	+++
Cardiac involvement	–	+[a]	++[a]	–	–	–	+
Myalgia	+++	+	–	–	++	–	–
Malignant hyperthermia	+++	++[b]	–	–	–	–	–
Histopathology							
Cores	+++	+++	+++	–	+	+	+
FTD	+	++	+	–	–	–	+
Connective tissue/fat	++	++	++	+	+	–	–
Central nuclei	++	++	–	+++	+++	–	–
Nemaline rods	+	+	–	–	–	+++	++

MTM1, myotubularin gene; *DNM2*, dynamin 2 gene; *NEB*, nebulin gene; *ACTA1*, skeletal muscle α-actin gene; *RYR1* ad, *RYR1* autosomal dominant; *RYR1* ar, *RYR1* autosomal recessive; –, not reported; +, infrequent; ++, common; +++, very common.

[a]Right ventricular impairment secondary to respiratory involvement.

[b]Exact risk of malignant hyperthermia susceptibility associated with recessive *RYR1* mutations currently unknown. [Reprinted from (3), with permission from Elsevier.

using a nontriggering anesthetic for all children with possible myopathies. There are subsets of metabolic and mitochondrial myopathies where agents such as propofol may not be advisable.

The future undoubtedly will bring major advances in the understanding of the ryanodine receptor and its role in MHS and core myopathies as well as in other muscle and nonmuscle diseases. Greater understanding of the genetics and pathophysiology of *RYR1* myopathies will lead to more clarity in providing anesthetic care for these children. There are early reports of therapies aimed at *RYR1* diseases (15). There is reason to hope that with greater understanding of the ryanodine receptor, these efforts will lead to not only therapeutic potential but also to reliable and confident anesthetic design.

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