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Review Article

RYR1-Related Myopathies and Anesthesiological Implications

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Abstract

Sequence variations in the *RYR1* gene encoding the skeletal muscle sarcoplasmic reticulum calcium release channel are the cause of malignant hyperthermia susceptibility and of several myopathies. This article reviews the *RYR1*-related myopathies and their association with malignant hyperthermia susceptibility, a life-threatening anesthetic complication which is avoidable if anticipated pre-surgically. This is especially important for counseling and improving patient safety during anesthesia, in particular for asymptomatic relatives of patients with recessive *RYR1*-related myopathies.

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ABBREVIATIONS

CCD: Central Core Disease; CFTD: Congenital Fiber Type Disproportion; CNM: Centronuclear Myopathy; KDS: King-Denborough Syndrome; MH: Malignant Hyperthermia; MmD: Multi-Minicore Disease; RYR1: Ryanodine Receptor Type 1; SV: Sequence Variation

INTRODUCTION

The skeletal muscle sarcoplasmic reticulum calcium release channel, commonly known as ryanodine receptor type 1 (RyR1), is encoded by the *RYR1* gene and specifically interacts with the voltage-dependent Ca^{2+}-channel Cav1.1, localized at T-tubular membrane. The depolarization of the plasma membrane results in conformational changes in Cav1.1, which are transmitted directly to the RyR1 channel, causing it to open. RyR1 and Cav1.1 are the two major proteins involved in the excitation-contraction (E-C) coupling in skeletal muscle. *RYR1* sequence variations (SVs) have been associated with several distinct skeletal muscle disorders, i.e., malignant hyperthermia susceptibility, central core disease, King-Denborough syndrome, late-onset axial myopathy, congenital "core-rod myopathy", with mainly autosomal dominant inheritance, and subgroups of multi-minicore disease, congenital fiber type disproportion, centronuclear myopathy, with autosomal recessive inheritance[1]. Autosomal-recessively inherited *RYR1*-related myopathies with wide clinico-pathological spectrum have emerged in recent years [2-4].

The present work reviews the *RYR1*-related myopathies and their association with malignant hyperthermia susceptibility, a life-threatening anesthetic complication which is avoidable if anticipated pre-surgically. This is especially important for counseling and improving patient safety during anesthesia, in particular for asymptomatic relatives of patients with recessive *RYR1*-related myopathies.

Malignant hyperthermia (MH)

Malignant hyperthermia (MH, OMIM # 145600) is a rare, pharmacogenetic disorder triggered by volatile anesthetics (halothane, isoflurane, desflurane, sevoflurane, enflurane) and/or depolarizing muscle relaxants (succinylcholine) in genetically predisposed subjects. In the absence of triggering agents, the affected individuals appear normal without specific pathologic signs. The MH-susceptibility (MHS) condition is transmitted as an autosomal dominant trait in man. On exposure to triggering agents MHS patients may experience an MH crisis as a consequence of an abnormally increasing of intracellular Ca^{2+} in skeletal muscle. The symptoms are skeletal muscle rigidity, metabolic acidosis, tachycardia and high temperature which correlate with altered biochemical parameters, such as increased pCO_2 and lactate production, hyperkalemia, release of muscle proteins, as creatine kinase and myoglobin, into the blood. Frequent late events are damage of kidney function due to massive myoglobin release and/or a diffuse intravascular coagulation, which is often the main cause of death [5]. The incidence of MH reactions is 1:5,000 to 1:50,000–100,000 anesthesias, and the estimated genetic incidence is 1:3,000 to 1:8,500 [5]. Advances in understanding the MH clinical manifestation and pathophysiology, and the treatment with dantrolene, an RyR1 antagonist that blocks Ca^{2+} release from the intracellular stores, resulted in much lower morbidity and mortality from MH; the mortality dropped from over 80% in the 1960s to less than 5%. Protocols for MH contracture testing of human skeletal muscle have been developed by the European [6] and North American [7] MH Groups, namely, *in vitro* contracture test (IVCT) and caffeine halothane contracture test (CHCT), respectively. MHS exhibits genetic heterogeneity, with 6 *loci* (MHS1, OMIM #145600; MHS2, OMIM %154275; MHS3, OMIM %154276; MHS4, OMIM % 600467; MHS5, OMIM# 601887; MHS6, OMIM %601888) so far implicated. Four (MHS2-MHS4, MHS6) of them have been

identified only in isolated European families. The MHS1 *locus* (*RYR1* gene) accounts for the majority of MHS cases (about 70%). Many different SVs of uncertain significance have been identified in the gene coding for RyR1, however only 31 RyR1 mutations have been proven to be causative for MH according to the criteria of the European Malignant Hyperthermia Group (www.emhg.org). Moreover, RyR1 SVs, associated or possibly associated to MHS status, have been identified in patients who experienced exertional rhabdomyolysis, and/or myalgia, and stress-induced MH events [8,9]. Less than 1% of MHS cases can be attributed to mutations in the *CACNA1S* gene (locus MHS5) encoding the alpha1S subunit of the Cav1.1 channel.. Only three MH-causing mutations identified in the *CACNA1S* gene were hitherto functionally characterized [10-12.].

Central core disease (CCD)

Central core disease (CCD, OMIM # 117000) is an autosomal dominant congenital myopathy characterized by motor developmental delay, hypotrophy and hypotonia in infancy (Table 1), although cases of adult onset have been reported [13]. Recessive transmission has been described for variant forms of CCD [4,14]. Weakness is typically proximal with prominent involvement of the hip girdle and axial muscles. The histological analysis of muscle samples with oxidative enzyme stains reveals the presence of central core lesions extending the length of type 1 muscle fibers. The cores are regions characterized by sarcomeric disorganization, absence of mitochondria, and lack of oxidative activity (Table 1). No association between the number of cores on muscle biopsy and the degree of muscle weakness has been described. *RYR1* disease-causing mutations have been identified in the majority of CCD cases. CCD patients are at risk of MHS: some patients experienced clinical episodes of MH and/or were typed MHS by IVCT.

King-Denborough syndrome (KDS)

King-Denborough syndrome (KDS) is a rare condition characterized by susceptibility to MH, hypotonia, delayed motor development, proximal weakness, short stature, cryptorchidism, skeletal abnormalities (scoliosis, kyphosis, lumbar lordosis, pectus carinatum/excavatum), and variable dysmorphic features (ptosis, down-slanting palpebral fissures, malar hypoplasia, micrognathia, high-arched palate, hypertelorism, low set ears). Muscle biopsies show myopathic features: fiber size variation and few, small, or atrophic type 1 muscle fibers and severe paucity of type 2 fibers (Table 1) [15,16]. The triad of MHS, dysmorphic features and myopathy is characteristic. KDS was first described by King and Denborough in 1973 [17], and only recently *RYR1* SVs have been identified in KDS patients [18-20]. All these SVs, but one [18], were non polymorphic, likely pathological and inherited from one parent. Moreover, reduced RyR1 protein expression has been detected in some KDS patients [20]. However, marked phenotypic variability associated with

Table 1: Clinical signs, inheritance and histochemistry of some *RYR1*-congenital myopathies.

Pathology	Clinical signs	Inheritance	Age at onset	Histochemistry	Serum CK
Central Core Disease, CCD	delayed motor development, hypotrophy and hypotonia, non-progressive weakness typically proximal	autosomal dominant*	infancy (adult onset also reported)	central cores of reduced oxidative activity, sarcomere disorganization, mitochondria depletion in type 1 fibers	usually normal
King-Denborough syndrome, KDS	hypotonia, delayed motor development, proximal weakness, short stature, cryptorchidism, skeletal abnormalities, dysmorphisms	autosomal dominant*	infancy	fiber size variation, few, small, or atrophic type 1 fibers, severe paucity of type 2 fibers	normal or moderately elevated
Core-rod myopathy	delayed motor development, lordosis, walking difficulties, weakness, Achilles' tendon contractures	autosomal dominant	infancy	central or eccentrically cores of reduced oxidative activity, multiple rods located in different areas of the cores	normal
Axial myopathy	slowly progressive, predominant axial muscle involvement, variable degrees of lumbar hyperlordosis, scapular winging and/or camptocormia, myalgia	autosomal dominant	adulthood (20-60 years)	fiber size variation, increased central nuclei, uneveneness of oxidative enzyme staining or central and eccentric cores	normal or moderately elevated (3-6 fold)
Fetal akinesia	decreased fetal movement, arthrogryposis, congenital dislocation of the hips, severe hypotonia	autosomal dominant / recessive	fetuses / infants	central cores,type 1 fiber predominance (dominant *RYR1* SVs), histologic heterogeneity (recessive *RYR1* SVs)	normal
Multiminicore disease, MmD	neonatal muscle hypotonia, delayed motor development, generalized muscle weakness, amyotrophy, external ophthalmoplegia	autosomal recessive	infancy or childhood	multicores of reduced oxidative activity, sarcomere disorganization, mitochondria depletion in most muscle fibers (type 1 and type 2)	normal
Centronuclear myopathy, CNM	neonatal hypotonia, reduced fetal movements, feeding difficulties, extraocular muscle involvement	autosomal recessive	birth, chilhood,	centrally located nuclei, predominance and hypotrophy of type 1 fibers	normal or slightly elevated
Congenital fiber type disproportion, CFTD	hypotonia, mild-to-severe generalized muscle weakness, ophthalmoplegia, ptosis, facial and/or bulbar weakness, limb/respiratory weakness	autosomal recessive	birth, chilhood	relative hypotrophy of type 1 muscle fibers compared to type 2 fibers	normal or mildly elevated

* cases with recessive inheritance have been described

some *RYR1* SV has been observed, even in patients/subjects of the same family with the same SV, i.e, parents harboring the same SVs of their KDS children are asymptomatic or are only MHS, or have a different myopathic picture. On the bases of these results, it has been advanced that "KDS is a digenic condition, with a *RYR1* mutation accounting for some aspects of the phenotype (susceptibility to MH and mild myopathy) and a second unrelated mutation causing other features like the dysmorphic facies" [20], not detected by routine sequencing methods. Moreover, patients with the KDS phenotype with either dominant or recessive inheritance have been reported [3].

Core-rod myopathy

Core-rod myopathy is a rare, genetically heterogeneous congenital myopathy characterized by the presence of cores and rods in distinct areas in the same or in different muscle fibers (Table 1). SVs in the *RYR1* gene [21-24] and in the skeletal muscle α-actin (*ACTA1*) gene [25] have been identified in families with autosomal dominant inheritance, and in the nebulin (*NEB*) gene in patients with autosomal recessive inheritance [26,27]. All the *RYR1* SVs identified in these patients lie in the transmembrane region of the RyR1 protein, in the Ca^{2+} channel-forming segment. One patient with Y4796C mutation in the RyR1 channel underwent IVCT and was typed MHS [21]. Patients presented with delayed motor development, lordosis, walking difficulties, weakness, Achilles' tendon contractures (Table 1) [21-23]. Moreover, monozygotic twins carrying the heterozygous *de novo* I4898T mutation in the RyR1 channel presented with a severe phenotype: polyhydramnios and loss of fetal motility during pregnancy, hypotonia, arthrogryposis and swallowing impairment at birth, and death before two months of life [24].

Late-onset axial myopathy

Heterozygous missense *RYR1* SVs have been reported in 12 patients with late-onset myopathy with predominant axial muscle involvement, variable degrees of lumbar hyperlordosis, scapular winging and / or camptocormia, myalgia (Table 1) [28,29]. The histological analysis of muscle samples revealed variability in fiber size, increased central nuclei, unevenness of oxidative enzyme staining [29] or central and eccentric cores (Table 1) [28,29]. Only one patient underwent the IVCT and was typed MHS.

Fetal akinesia

RYR1 SVs have been identified in 15 patients (fetuses/infants) with decreased fetal movement, arthrogryposis, congenital dislocation of the hips, skeletal and feet deformities, severe hypotonia, respiratory insufficiency at birth (Table 1) [30,31]. Both dominant (6 cases) and recessive (9 cases, compound heterozygous) inheritance of the *RYR1* SVs has been reported [30-32]. The histological analysis of muscle samples revealed the presence of central cores and type 1 fiber predominance in patients with dominant *RYR1* SVs and histological heterogeneity in patients with recessive *RYR1* SVs (Table 1).

Multi-minicore disease (MmD)

Multi-minicore disease (MmD, OMIM #255320) is a recessive clinically heterogeneous condition; general features include neonatal muscle hypotonia, delayed motor development, generalized muscle weakness, and amyotrophy (Table 1). Muscle biopsy shows multiple areas (minicores) of reduced oxidative activity, sarcomere disorganization and mitochondria-depletion in most muscle fibers (Table 1). Clinical presentation in MmD is variable with four subtypes described [33]. MmD is genetically heterogeneous: the classic phenotype characterized by spinal rigidity, early scoliosis and respiratory impairment is due to recessive mutations in the selenoprotein N (*SEPN1*) gene, whereas recessive *RYR1* SVs –homozygous or compound heterozygous- have been identified in patients with a wide range of clinical features including external ophthalmoplegia, distal weakness and wasting or predominant hip girdle involvement (Table 1). MH episodes of MmD patients with recessive *RYR1* SVs have been reported [33].

Centronuclear myopathy (CNM)

Centronuclear myopathy (CNM) is a congenital condition with genetic heterogeneity and highly variable clinical phenotypes. X-linked forms have a severe phenotype presenting in males at birth with marked weakness and hypotonia, external ophthalmoplegia and respiratory failure, autosomal dominant forms have a later onset and milder course, and autosomal recessive forms are intermediate. Extraocular muscle involvement is common in all forms of CNM. The X-linked form [OMIM, #310400] is caused by mutations in the myotubularin (*MTM1*) gene, the autosomal-dominant form [OMIM, #160150] by mutations in the dynamin 2 (*DNM2*) gene, and the autosomal recessive forms by mutations in the amphiphysin 2 (*BIN1*) gene [OMIM, #255200] or in the *RYR1* gene. The histological picture of CNM muscle biopsies is characterized by prominence of central nuclei and predominance and hypotrophy of type 1 fibers [34] (Table 1). Patients with a severe phenotype and recessive *RYR1*-CNM have been recently described [2,35]; no MH reactions have been reported in these patients and they were not typed by IVCT.

Congenital fiber type disproportion (CFTD)

Congenital fiber type disproportion (CFTD, OMIM #255310) is characterized by hypotonia and mild-to-severe generalized muscle weakness at birth or within the first year of life (Table 1). CFTD is genetically heterogeneous with six genes involved: alpha actin (*ACTA1*) gene (~6% of CFTD cases), myosin heavy chain 7 (*MYH7*) gene (rare) , *SEPN1* gene (rare), tropomyosin 2 (*TPM2*) (rare) and 3 (*TPM3*) (~20%-25% of CFTD cases) genes, and *RYR1* gene (10%-20% of CFTD cases). The skeletal muscle histological pattern is characterized by relative hypotrophy of type 1 muscle fibers compared to type 2 fibers (Table 1). No family history of MH has been reported in *RYR1*- CFTD families [36].

Autosomal-recessive *RYR1*-related myopathies with wide clinic-pathological spectrum

In recent years an increasing number of myopathy cases with recessive *RYR1* SVs and non-specific histological features has been reported [3,4]. Moreover, a homozygous *RYR1* SV has been identified in a family with benign Samaritan congenital myopathy [37] and *RYR1* SVs at homozygous or at compound heterozygous status have been found in two families with ophthalmoplegia without definite skeletal myopathy [38].

DISCUSSION AND CONCLUSION

In recent years, a wide range of clinical and histopathological variants have been associated with *RYR1* SVs; therefore, it has been advanced that *RYR1*-related myopathies are probably the most frequent form of congenital myopathies in several populations [3,39,40]. The inheritance of *RYR1*-related myopathies is complex and high phenotypic variability is associated with some *RYR1* SVs, even in patients of the same family with the same SV and in the same individual at different ages. Considering the genetic heterogeneity of congenital myopathies and the possible association of *RYR1*-related myopathies with MHS, the recognition of the genetic bases of myopathies is essential; an approach to the differential diagnosis of congenital myopathies has been recently reported [41]. When indicated, the identification of *RYR1* SVs is crucial for counseling and improving patient safety during anesthesia, in particular for asymptomatic relatives of patients with recessive *RYR1*-related myopathies. In fact, some *RYR1* SVs found at the homozygous or at compound heterozygous state in patients with recessive myopathies have been reported at a heterozygous level in several MHS patients, and may determine dominantly inherited susceptibility to MH in heterozygous unaffected relatives [4,19]. Therefore, the affected patients and their carrier relatives should be aware of the potential risk of MHS, and possibly undergo the IVCT. In conclusion, it may be advisable to provide non-MH triggering anesthesia to patients with *RYR1*- related myopathies and their relatives until definitive diagnostic IVCT can be performed.

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