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CLINICAL REPORT

A family with discordance between malignant hyperthermia susceptibility and rippling muscle disease

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Abstract Rippling muscle disease (RMD) is a disorder that affects striated muscle and involves disturbances in calcium homeostasis. Malignant hyperthermia susceptibility (MHS) is a potentially lethal disorder, characterized by extreme hypermetabolism and muscle rigidity/rhabdomyolysis during anesthesia with potent inhalational agents, in otherwise healthy individuals. The aim of this report was to search for a correlation between RMD and MHS in members of a family in which both disorders were present. Ten members of a large Swedish family segregating RMD were tested for MHS prior to establishing an RMD diagnosis. Results from diagnostic RMD investigations and anesthesia outcomes were collected and cross-referenced to evaluate whether phenotype variations could be predicted by in vitro contracture test (IVCT) results suggestive of MHS. No correlation was found between individual RMD phenotypes and the IVCT results. There were no recorded adverse reactions to anesthesia, and RMD and MHS did not co-segregate. We conclude that RMD patients should not, on the basis of our present knowledge, be classified as having MHS; however, an increased surveillance for MH reactions is recommended in these patients.

Keywords Caveolin 3 · Malignant hyperthermia susceptibility · Rippling muscle disease · Calcium · Anesthesia

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Introduction

Rippling muscle disease (RMD) is a disorder of striated muscle that belongs to the caveolinopathies—a spectrum of muscular disorders caused by mutations in the *CAV*3 gene encoding caveolin 3 [1, 2]. RMD was first described in 1975 as an autosomal dominant disease [3]. Patients may suffer from slight muscle stiffness and soreness, and muscle strength can be normal. Tapping of skeletal muscle typically causes rapid contractions, muscle mounding, and the rippling phenomenon that gives the disease its name [4]. These muscle phenomena are usually electrically silent on an electromyogram (EMG) [5, 6]. Serum creatine kinase (CK) is usually elevated.

Malignant hyperthermia (MH) susceptibility (MHS) is a potentially fatal disorder that can cause an MH reaction, characterized by fulminant hypermetabolism and muscle rigidity/rhabdomyolysis triggered by inhalational anesthetics in otherwise healthy individuals [7]. MHS is most often caused by mutations in the *RYR*1 gene [8], which encodes the skeletal muscle cell ryanodine receptor (RyR), a calcium-release channel located in the membrane of the sarcoplasmic reticulum [9]. A mutation in the *CACNA*1S gene, encoding the α1 subunit of the dihydropyridine-sensitive L-type voltage-dependent calcium channel (DHPR), has also been associated with MHS [10].

MHS is inherited in an autosomal dominant pattern. The prevalence of causative mutations could be as high as 1 in 3000 [7]. A negative mutation analysis cannot exclude MHS [11].

Although no cases of fulminant MH or other anesthetic complications have been described in connection with RMD, patients with *CAV*3 mutations might be at risk for MH reactions, because caveolin 3 is involved in calcium homeostasis [2, 8]. For this reason, the use of non-triggering agents has been recommended for patients with isolated hyperCKemia [12]. Here we describe a large family with RMD and MHS. We cross-referenced the outcomes of anesthesia and the diagnostic investigations in this family to evaluate whether phenotype variations predicted MHS.

Case report

Ten individuals with RMD from a family containing 23 affected members were investigated for MHS (Fig. 1) [13]. The diagnosis of RMD was based on clinical characteristics, neurophysiological studies including EMG, muscle biopsy in selected individuals, and sequencing of the *CAV*3 gene [13].

A p.A46T mutation in the *CAV*3 gene was identified in all 10 individuals with RMD.

The MHS proband (patient no. 2; number as given in Fig. 1) had a history of suspected myocarditis, muscular fatigue, muscle cramps, hyperCKemia, and a 5- to 10-min episode of generalized muscle stiffness elicited by local anesthesia during childhood. He was investigated by an in vitro contracture test (IVCT) and diagnosed with MHS. The IVCT was performed according to the European Malignant Hyperthermia Group protocol [14]. Nine additional family members were then given the IVCT. No genetic analysis for MH-causing mutations was performed in any of the family members.

Clinical data on the outcome of general anesthesia were collected from patient histories and medical files in all family members with RMD, including those not given the IVCT ($n = 17$). We cross-referenced these data with the IVCT test results and the clinical diagnostic data on RMD, with the aim being to establish a putative correlation between RMD and the IVCT results suggestive of MHS.

The study was approved by the regional ethics committee and written consent was obtained from all participants.

Twenty-three members of the family presented here had previously been diagnosed as having RMD (Fig. 1) [13]. Ten family members had been investigated concerning both RMD and MHS by the IVCT (Table 1). Six of these individuals showed clinical signs of RMD and carried the *CAV*3 p.A46T mutation, and four of these six had pathological IVCT results (Table 1). Two of the four individuals with no evidence of RMD were diagnosed as having MHS.

One patient with a pathological IVCT result (reaction to halothane) had received general anesthesia with MH-triggering agents twice without adverse effects (patient no. 8). His mother, who was diagnosed with RMD but not tested by the IVCT, had undergone surgery with exposure to MH-triggering agents on numerous occasions.

Eight RMD patients not given the IVCT had undergone surgery with general anesthesia induced by MH-triggering agents. In total, at least 18 exposures to MH-triggering agents were identified in the histories of these patients. No adverse events were recorded.

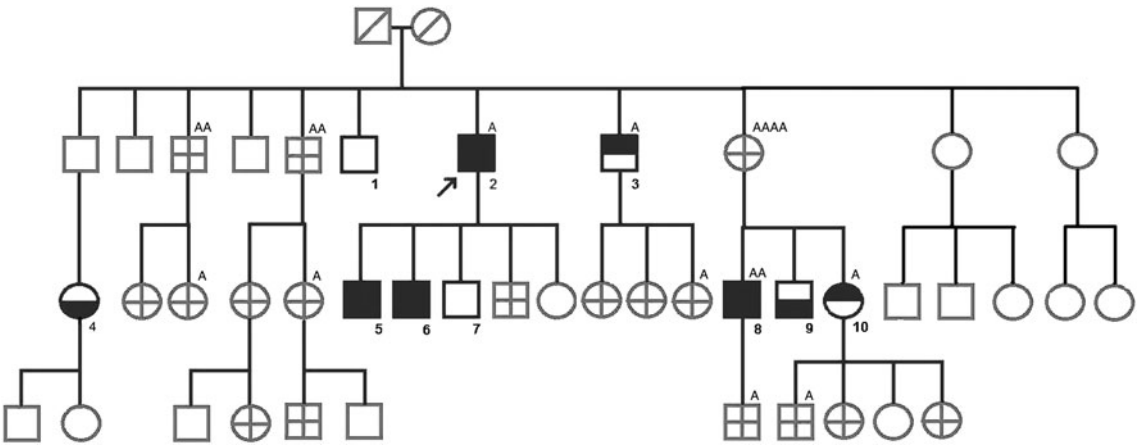

Fig. 1 Pedigree of the investigated family. *Cross symbols in gray* represent patients with rippling muscle disease (RMD) who have not been tested with the in vitro contracture test (IVCT) for malignant hyperthermia susceptibility (MHS). *Arrow* denotes the MHS proband. Patients who have been tested with the IVCT are *numbered and presented* in *black*. *Numbers* refer to data in Table 1. *Lower halves of filled symbols* represent MHS, *upper halves of filled symbols* represent RMD. *Capital A letters above and to the right of the symbols* represent number of exposures to inhalational anesthetic agents

Table 1 Summary of the results of the ten patients who were investigated for both rippling muscle disease (RMD) and malignant hyperthermia (MH) susceptibility

Patient number	IVCT diagnosis	RMD	Creatine kinase (CK) value (μkat/l)	Caffeine contracture (g)	Halothane contracture (g)	Threshold caffeine (mM)	Threshold halothane (%)
5	S	Yes	60.2	0.3	0.5	2	2
9	S	No	1.0	0.4	0.7	1.5	1
6	S	Yes	44.7	0.5	1.1	2	2
4	S	No	0.5	0.4	0.8	2	2
2	Eh	Yes	8.6	–	0.4	–	2
8	Eh	Yes	3.9	–	0.4	–	2
1	N	No		–	–	–	–
3	N	Yes	9.8	–	–	–	–
10	N	Yes	4.3	–	–	–	–
7	N	No		–	–	–	–

S denotes MHS (malignant hyperthermia-susceptible), muscle bundles react with contracture of ≥0.2 g in the in vitro contracture tests (IVCTs) for halothane and caffeine, respectively; *Eh* denotes MHEh (malignant hyperthermia-equivocal), muscle bundles react with contracture of ≥0.2 g in the IVCT halothane test; *N* denotes MHN (malignant hyperthermia-negative), no muscle bundles react with contracture. MHS and MHEh are clinically considered MH-susceptible. The use of MH-triggering agents is contraindicated

The clinical phenotype of RMD was similar in all patients irrespective of the result of the IVCT.

Discussion

Skeletal excitation–contraction coupling is a pivotal process in the physiology of skeletal muscles. The proteins caveolin 3, RyR, and DHPR are all involved in this process [15]. There are functional links between RMD and MHS because caveolin 3 interacts with the transmembrane domain of RyR and can affect the function of DHPR [16–18]. This channel acts as a voltage sensor for RyR and also regulates the slow Ca^{2+} current from the extracellular space [17]. DHPR mediates the Ca^{2+} influx caused by plasma membrane depolarization, a process that is dependent on RyR [19]. A decrease of Ca^{2+} influx in isolated human RMD myotubes has been found, as well as a loss of co-localization of RyR and DHPR [20]. A disruption of the RyR-DHPR complex may underlie the increased muscular mechanosensitivity of RMD patients [21]. Dantrolene sodium, which is used to treat fulminant MH reactions, is an effective drug to relieve the muscle stiffness associated with RMD, but it can also exacerbate weakness [5]. Dantrolene dissociates excitation–contraction coupling by interfering with the release of Ca^{2+} from the sarcoplasmic reticulum [22]. Due to high vigilance and the use of dantrolene, the mortality of MH reactions has dropped from over 80% to <5 % during the past three decades [7].

Although other channelopathic myotonias are functionally linked to MH, MH reactions have not as yet been reported in any of them [23]. The hyperirritable nature of muscle cells in RMD patients may give a false-positive IVCT result. Another hypothesis is that increased intracellular calcium concentrations in the skeletal muscles of RMD patients may induce MH reactions, although there is no evidence to support this.

In 105 patients with fulminant MH reactions and 202 control patients, the specificity of the IVCT was 94 % and the sensitivity 99 % [14]. Thus, the possibility that two individuals from the same family, as described in the present study, would present a false-positive test result is very small. The most likely explanation for our findings is a segregation of two different hereditary diseases in this family, both affecting muscle cell irritability.

It is important that the diagnosis of MHS be reserved for patients truly at risk for MH reactions. In spite of its high specificity and sensitivity, it should also be taken into account that the IVCT was validated in populations without neuromuscular disorders [24].

The present study does not exclude a connection between RMD and MHS. RMD is a rare disorder with, in many cases, a mild phenotype that may go unnoticed for many years. In addition, MHS families may also go unnoticed, because fulminant reactions occur in only 6.5 % of MHS subjects and may not develop at the first exposure [7]. Whether RMD patients are susceptible to other anesthetic complications such as succinylcholine-induced hyperkalemia and/or rhabdomyolysis is unknown, but succinylcholine should be avoided in all myopathies. We wish to point out the implications of falsely labeling individuals carrying a benign trait such as RMD as having an increased risk of a rare but life-threatening event, because this can cause unnecessary anxiety and have a negative impact on social and professional life. There are also situations where the exclusion of MH-triggering drugs may

increase a patient's general anesthetic risk; for example, the use of inhalational anesthetics in patients with a high airway obstruction. Our findings do not warrant the automatic labeling of RMD patients as having MHS. As pointed out by Benca and Hogan [25], a prudent approach in this and similar situations is warranted.

To conclude, patients with RMD should not as of now be classified as having MHS, but anesthesiologists should be aware of the condition, observe increased surveillance, and act promptly if signs of MH are noticed.

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Conflict of interest The authors have no conflict of interest relevant to the context of this study.

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