Anesthesiology 2010; 112:239–44

Exertional Rhabdomyolysis and Malignant Hyperthermia in a Patient with Ryanodine Receptor Type 1 Gene, L-type Calcium Channel α-1 Subunit Gene, and Calsequestrin-1 Gene Polymorphisms

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THE relationship between hypermetabolic exertional stress injuries and malignant hyperthermia (MH) has been a topic of debate for almost 30 yr. Central to this debate is the idea that some MH susceptible (MHS) patients may develop awake nonanesthesia-related manifestations similar to that seen in porcine stress syndrome.[1–7] Although a link has never been established by controlled clinical studies, individual case reports and a small number of clinical series support an association between unexpected exertional rhabdomyolysis (ER) and MH susceptibility,[8] two syndromes characterized by abnormal intracellular skeletal muscle calcium regulation.[9,10]

An individual is identified as MHS if he or she has a well-documented clinical episode consistent with MH during exposure to any of the known anesthetic triggering agents, or if he or she has undergone a skeletal muscle biopsy with a positive diagnostic contracture test. However, none of the published reports of patients who presented first with ER and who were subsequently identified as MHS by a positive contracture test ever developed documented clinical MH episodes involving anesthesia.[11–16] We present a case that is compelling for two reasons. First, it is the only documented case of an individual who presented first with ER, followed by a clinical MH episode during anesthesia, and then by a positive contracture test. Second, genetic analysis revealed the presence of variants in the ryanodine receptor type 1 gene (*RYR1*), the L-type calcium channel α-1 subunit gene (*CACNA1S*), and the calsequestrin-1 gene (*CASQ1*). This report provides clinical evidence for an association between ER and MH and discusses the possible role for synergistic action among rare variants in the genes encoding proteins crucial to skeletal muscle calcium regulation.

CASE REPORTS

A physically fit, muscular, 30-yr-old, 93-kg African American presented to the emergency department with intense bilateral calf pain after a 2.5-mile walk. He had a history of bilateral patella syndrome and was diagnosed with an acute exacerbation. Rest, diazepam, and oxycodone/acetaminophen were prescribed. His medical history was significant for hypertension and hyperlipidemia treated with hydrochlorothiazide (25 mg daily) and simvastatin (20 mg daily), respectively. Simvastatin was prescribed approximately 1 month before this episode, and he provided no history consistent with statin-induced myopathy or episodes of ER. The calf pain increased in intensity over the ensuing week after which he was re-presented to the emergency department and was diagnosed with ER (creatine kinase [CK] > 10,000 U) and bilateral calf compartment syndrome, requiring surgical fasciotomies. Preoperative toxicology screen test results were negative for methadone, amphetamines, barbiturates, cannabinoids, cocaine, phencyclidine, benzodiazepines, and opiates, despite having been prescribed diazepam and oxycodone. There were no other medications identified in this patient, which are associated with rhabdomyolysis. Complete blood count, electrolytes, and urine myoglobin were normal. Procedures to rule out lower extremity vascular lesions were not performed. Before surgery, he denied a personal or family history of MH, use of dietary supplements, and heat intolerance. However, he did report occasional muscle cramping.

Bilateral four-compartment lower extremity (calves) fasciotomies were performed with general endotracheal anesthesia. General anesthesia was induced with intravenous midazolam (4 mg), fentanyl (200 μg), lidocaine (50 mg), propofol (180 mg), rocuronium (10 mg) and succinycholine (100 mg), followed by the placement of an 8.0 endotracheal tube. Anesthesia was maintained with intravenous fentanyl (350 μg total dose), and inhaled nitrous oxide (50%), oxy-

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Received from the Department of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland. Submitted for publication April 29, 2009. Accepted for publication August 26, 2009. Supported by grant No. R080CD from the Uniformed Services University of the Health Sciences (to Dr. Sambuughin) and P01 AR052354-01A1 from the National Institutes of Health, Bethesda, Maryland (to Dr. Muldoon).

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gen (50%), and sevoflurane (2.4%). At the completion of surgery, no neuromuscular reversal agents were administered, inhalational anesthetics were discontinued, the oropharynx was suctioned, and the patient was extubated and recovered without complication. During the procedure, the heart rate ranged from 98 to 105 beats/min, blood pressure ranged from 110 to 130 mmHg over 60 to 80 mmHg, and end-tidal carbon dioxide ranged from 30 to 40 mmHg with pressure-controlled minute ventilation ranging from 6.0 to 6.8 l/min. The esophageal temperature ranged from 36.5° to 37.1°C. Because the patient had an allergy to penicillin, clindamycin (600 mg, intravenously) administration was begun before incision and completed within 45 min.

One day later, he returned to the operating room for a 30-min irrigation and debridement of his fasciotomy wounds. His serum CK had decreased from 10,609 U on the day of admission to 3,842 U. Before the second surgery, he was afebrile (37°C), tachycardic (110 beats/min), hypertensive (187/117 mmHg), and complained of intense calf pain. Although the tachycardia and hypertension might have been signs of other metabolic causes, it was thought to be secondary to pain, as the surgeons requested conservative postoperative pain management out of fear that high opioid or epidural analgesia might mask a worsening compartment syndrome. Midazolam (2 mg, intravenously) and fentanyl (100 μg, intravenously) helped to reduce the pain, but had no immediate effect on the tachycardia and hypertension. In the operating room, he was preoxygenated, and general anesthesia was induced with intravenous propofol (200 mg). Isoflurane (1%) was administered after placement of a #4 *Laryngeal Mask Airway*™ (The Laryngeal Mask Company Limited, Le Rocher, Victoria, Mahe, Seychelles). Spontaneous ventilation was confirmed *via* breath sounds and capnography, and he was transferred from his hospital bed to the operating table while anesthesia was maintained with isoflurane and 100% oxygen. No depolarizing or nondepolarizing neuromuscular blocking agents were administered.

Total body rigidity developed of sufficient severity that the patient's arms could not be abducted and placed on arm boards. The surgeon likewise remarked at how stiff the patient's legs had become. The capnography reading was then lost as the patient developed severe trismus, occluding the *Laryngeal Mask Airway*™. Heart rate increased to 128 beats/min. Inadequate anesthesia was suspected, so the isoflurane was increased to 2% and another 150 μg of intravenous fentanyl was administered. Forceful manual ventilation was begun *via* the partially occluded *Laryngeal Mask Airway*™ and end-tidal carbon dioxide reappeared on the capnograph. The nasal temperature probe registered 38.5°C. There were no signs of an infectious etiology, and the patient was not being externally warmed. Spontaneous ventilation resumed at 20–22 breaths/min, despite total doses of 2 mg midazolam, 250 μg fentanyl, 200 mg propofol, and 2% isoflurane. End-tidal carbon dioxide increased as high as 70 mmHg, but it was unclear whether this was due to hypoventilation through a partially occluded *Laryngeal Mask Airway*™ or the result of a hypermetabolic phenomenon.

Isoflurane was discontinued, 100% oxygen was delivered at a rate of 10 l/min, and total intravenous anesthesia was started with 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol. The rigidity resolved and end-tidal carbon dioxide decreased to 55 mmHg with a spontaneous respiratory rate of 12–15 breaths/min. Nasal temperature decreased from 38.5° to 38.1°C. Tachycardia and hypertension resolved with intravenous metoprolol (5 mg). Although a diagnosis of MH was considered, the presentation was unclear, especially because the signs of MH appeared to resolve with the administration of a propofol infusion and metoprolol. Thus, arterial blood gases were not obtained, nor was dantrolene administered at this point. However, the plan was to closely observe the patient for any suspicious signs of MH. The case was concluded within 20 min without further complication, and the patient was extubated and transferred to the postanesthesia care unit for close observation.

Initial oral temperature in the postanesthesia care unit was 37.7°C. Although pain was well controlled, tachycardia (110) and hypertension (170/100) returned and did not respond to labetalol (30 mg intravenously over 30 min). Within 45 min of entering the postanesthesia care unit, oral temperature had risen to 39.4°C. A radial arterial catheter was placed, and arterial blood gases and CK were ordered. The arterial blood gases were 7.404/44.3/118/3/27.7/99% and CK was 4,197 U. Serum potassium had increased to 4.8 mM, compared with 4.0 mM on the morning before surgery. The patient was transferred to the surgical intensive care unit and given an intravenous bolus of dantrolene (240 mg) approximately 1.5 h after signs of MH first appeared during anesthesia induction. Two hours after the dantrolene loading dose, rectal core temperature was still 39.7°C, and the serum potassium was 5.4 mM. Consistent with the recommended management of MH, a second dose of intravenous dantrolene (1 mg/kg) was given because the fever had not resolved. During the next several hours, serial CKs showed a decline, and by the next morning, rectal core temperature was 37.1°C. Urine myoglobin was negative. Thyroid panel and metanephrines were normal, and no further workup was ordered for thyroid disease and pheochromocytoma. Retrospectively, the MH clinical grading scale was used, and a score of 53 was calculated for a rank of 6 and qualitative likelihood of "almost certain."[17]

Six months later, the patient underwent a left *vastus lateralis* muscle biopsy for MH testing with a caffeine halothane contracture test (CHCT). The CHCT result was positive for 3% halothane (0.7, 0.9, and 0.6 g of tension in three separate muscle strips), but negative for caffeine.[18] Although these results are considered MHS by North American MH standards, the negative response to caffeine constitutes an MH equivocal diagnosis by European standards.[19] Despite the discontinuation of statin therapy and reporting no sequelae, the patient's baseline CK at the day of the biopsy was 417 U (normal, 50–200 U). Standard muscle histology testing showed mild denervation atrophy. As a part of an ER evaluation, an Exercise Intolerance Mutation Panel test (Robert Guthrie Biochemical and Molecular Genetics Laboratory, Buffalo, NY) was performed. This DNA blood test screens for the most common mutations in the *CPT2* (S113 l, Q413fs, P50H, G549D), *PYGM* (R50X, G205S) and *AMPD1* (Q12X, P48 l) genes, which code for enzyme deficiencies in carnitine palmitoyltransferase II, myophosphorylase, and myoadenylate deaminase, respectively.[20] In addition, a Myoglobinuria Evaluation test (Athena Diagnostics,

Inc., Worcester, MA) was performed on frozen muscle obtained at the time of the biopsy. Specifically, this evaluation tests for enzymatic deficiencies in phosphorylase A, phosphorylase b kinase, myoadenylate deaminase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, carnitine palmitoyltransferase II, and glycogen.[20] Both the Exercise Intolerance Mutation Panel and Myoglobinuria Evaluation test results were negative.

With approval of the Institutional Review Board of the Uniformed Services University of the Health Sciences (Bethesda, Maryland), written informed consent was obtained from the patient to sequence the entire coding regions for the *RYR1*, *CACNA1S*, and *CASQ1* genes. Sequencing was performed using complementary DNA transcribed from messenger RNA extracted from muscle to capture intronic mutations that have splicing effects. Complete sequencing of *RYR1* and *CASQ1* was performed as described by Sambuughin *et al.*[21] In brief, the complementary DNA was synthesized using messenger RNA extracted from muscle and amplified in 2 and 25 overlapping fragments for *CASQ1* and *RYR1*, respectively. Primers used for this purpose were designed using Primer 3 software.‖ The sequence variants were determined by direct sequencing of polymerase chain reaction fragments using an ABI 3100 DNA analyzer (Applied Biosystems, Foster City, CA). Direct sequencing of the polymerase chain reaction product was performed in one or both directions depending on sequencing results.

Gene sequencing revealed *RYR1* variant Ser1342Gly in exon 28, *CACNA1S* variant Leu1800Ser in exon 44, and *CASQ1* variant His66Arg in exon 1. All polymorphisms were heterozygous. No splice variants were found. Genetic testing was not performed in the patient's parents or close relations. Both *RYR1* and *CACNA1S* variants found in this patient are reported in the public database (Single Nucleotide Polymorphism, National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD). The Leu1800Ser *CACNA1S* variant is most common in African Americans (frequency range, 0.46–0.60), followed by Asians (0.15) and Caucasian (0.08). The Ser1342Gly *RYR1* variant, however, is rare and identified only in the African American population with a frequency of 0.04. The frequency of the *CASQ1* His66Arg variant identified in this study was estimated in healthy controls representing three ethnic groups: African Americans (N = 70), Caucasian Americans (N = 80, including 50 MH negative by CHCT), and Asians (Chinese and Mongolians, collected from mainland Asians with no intervening generation of ancestors resident in North America, N = 50). Ethnicity for controls was determined by self-report (mixed heritage unknown). There was no bias in identifying the population of the samples tested. All controls had been collected for previous similar studies[21,22] and were made available for this study without personal identification. With approval of the Institutional Review Board of the Uniformed Services University of the Health Sciences, written informed consent was obtained from controls to use their tissue for any scientific purpose involving any approved future project. Caucasian Americans and Asian controls tested negative for the *CASQ1* His66Arg variant. Three African American controls contained the variant, providing an estimate for allele frequency at 0.02 among this population.

‖ http://frodo.wi.mit.edu/primer3/. Accessed December 2, 2008.

Discussion

Rhabdomyolysis is a potentially fatal clinical syndrome caused by the dissolution and disintegration of striated muscle. The diagnosis is based on a complaint of muscle pain or weakness in the presence of elevated serum CK. Severe or untreated cases may result in life-threatening hyperkalemia, myoglobinuria, renal failure, and multiorgan system failure.[9] The etiology of rhabdomyolysis is diverse, and its actual incidence is unknown.[23] Rhabdomyolysis is under-reported at approximately 26,000 cases in the United States each year, accounting for 5–7% of all cases of acute renal failure.[9] The true incidence is likely much higher.

ER is a frequent complication of exertional heat illness, but can occur in the absence of high environmental or core body temperatures. ER occurs in response to strenuous eccentric exercise when mechanical or metabolic stress damages skeletal muscle.[23] Although the diagnostic criteria for ER are somewhat controversial, clinical practice guidelines typically define rhabdomyolysis as a serum CK greater than or equal to five times the upper limit of normal.[23] Under extreme physical and environmental conditions anyone may develop ER.[9] However, some individuals seem to be more predisposed than others, suggesting a metabolic myopathy or genetic link.[23] The differential diagnosis for ER is extensive and beyond the scope of this article. For a more complete discussion on the differential, the reader is referred to any of the referenced review articles.[9,23]

Typically, MH is a subclinical myopathy characterized by a hypermetabolic syndrome during and after anesthesia that is often inherited as a Mendelian trait. *RYR1* and *CACNA1S*, the only genes thus far identified to be associated with MH,[24,25] encode proteins integral to the fast release calcium channels in the sarcoplasmic reticulum of skeletal muscle. MH reactions are related to skeletal muscle calcium dysregulation triggered by halogenated inhalational anesthetics or succinylcholine.[10] Manifestations of an MH crisis can include skeletal muscle rigidity, mixed metabolic/respiratory acidosis, tachycardia, hyperpyrexia, rhabdomyolysis, hyperkalemia, elevated CK, multiorgan system failure, disseminated intravascular coagulation, and death.[10] However, MH is a syndrome characterized by variable expression and incomplete penetrance. Hence, individuals often do not develop clinical MH episodes with every exposure to anesthetic triggering agents, nor is the temporal and clinical expression of the syndrome uniform. Because previous safe anesthesia with MH triggering agents does not guarantee future safety, any signs of unexplained hypercarbia, tachydysrhythmia, trismus, rigidity, fever, and partial improvement when volatile agents are discontinued should prompt anesthesia providers to obtain appropriate laboratory tests expeditiously.

Shared features of ER and MH are hypermetabolic states that include a high demand for adensosine triphosphate, accelerated oxidative, chemical and mechanical stress of muscle, and an uncontrolled rise in intracellular calcium. These processes overwhelm the normal cellular regulatory mechanisms, and severe muscle injury and death occurs in certain individuals. These similarities have raised the possibility that ER and MH are related syndromes triggered by different mechanisms. Lopez *et al.* showed that calcium was increased in muscle fibers from patients with ER. Moreover, dantrolene, a known inhibitor of calcium release from the sarcoplasmic reticulum and the only antidote for MH, decreased myoplasmic calcium in ER patients and improved clinical outcomes.[26]

Diagnostic testing for MH susceptibility, specifically the *in vitro* contracture test (IVCT, validated test used in Europe) and CHCT (validated test used in North America), has been used to determine the MHS status of ER patients. Although the idea that stress- or exercise-induced awake episodes of MH similar to that seen in porcine stress syndrome was suggested nearly 30 yr ago,[1–7] the first series of patient data that described an association between unexplained ER and positive IVCT was reported in 1991.[12,13] Since then, there have been multiple cases reported of individuals with ER who have positive CHCT or IVCT, some of whom have *RYR1* variants.[11,16] The most relevant publication on this topic is by Wappler *et al.*,[11] in which 10 of 12 unrelated ER patients without personal or family histories of MH were IVCT positive, and 3 of the 10 IVCT positive patients were found to have known *RYR1* causative mutations. However, no episodes of intraoperative MH ever followed the initial presentations and diagnoses of ER. Although these reported ER cases met the laboratory criteria for MH susceptibility, none met the clinical criteria, until this report.

Unfortunately, there are several drawbacks in using IVCT or CHCT methodology in the evaluation of ER. For one, the specificity of the CHCT is 78%.[27] With a false-positive rate of 22%, the CHCT diagnoses some normal patients as MHS and captures some non-MHS-related myopathies.[28,29] The CHCT and the IVCT were validated specifically for clinical MH during anesthesia and not for clinical ER. Thus, to identify an ER patient without a clinical history of MH as MHS because they met the laboratory criteria (positive IVCT or CHCT) is problematic. Some ER patients may be classified as MHS by contracture testing, but this does not mean that a causal relationship is proven. Furthermore, European IVCT and North American CHCT standards differ in that a positive muscle contracture response to either halothane or caffeine is considered MHS in North America, but MH equivocal in Europe.[18,19] The support for an association between exertional heat illness and MH susceptibility is evidenced by recent studies in Y522S RyR1 knockin mice. These mice transfected with a human MH gene mutation developed muscle contractures, rhabdomyolysis, and death in response to elevated environmental temperatures.[30] However, these same mice did not develop rhabdomyolysis when muscle was subjected to repeated bouts of eccentric contractions when core temperature was maintained at lower physiologic temperatures during exercise.[31] Although promising, these studies represent a nonhuman model of only one human *RYR1* mutation of over 170 human *RYR1* variants that have been identified.[32]

Despite the great advances in genetic analysis, only 50–70% of MHS patients harbor an *RYR1* mutation,[32] and less than 1% for *CACNA1S*.[33] Thus, it is speculated that there are other, yet unidentified, gene mutations that confer MH susceptibility. *CASQ1* has recently been identified as another possible gene candidate.[34,35] *CASQ1* encodes calsequestrin-1, a moderate-affinity, high-capacity calcium-binding protein in the sarcoplasmic reticulum terminal cisternae of skeletal muscle. Calsequestrin-1 functions as both a calcium-binding protein and a luminal regulator of ryanodine receptor (RyR1)-mediated calcium release.[35] Calsequestrin-1-knockout mice developed anesthetic- and heat-induced sudden death in response to either 2% halothane or heat stress triggers. Furthermore, these mice developed whole-body contractures, elevated core temperature, and severe rhabdomyolysis, which was prevented by previous dantrolene administration.[35]

It is unclear what the genetic changes in the *RYR1* (Ser1342Gly), *CACNA1S* (Leu1800Ser), and *CASQ1* (His66Arg) mean in this case, because they occur at frequencies of 0.04, 0.46, and 0.02, respectively, in African American controls. The *RYR1* and *CASQ1* variants are rare polymorphisms identified only in African American controls. *CASQ1* His66Arg is a novel variant and His at position 66 of the protein is conserved across different species of skeletal and cardiac muscle calsequestrins. It is interesting to note that the Ser1342Gly *RYR1* variant was initially reported in association with MHS in a Caucasian (European) patient[32] and in another nonrelated MHS patient (Thierry Girard, M.D., Associate Professor, Department of Anesthesia, University Hospital of Basel, Switzerland, written personal communication, August 2008). Similar to our patient, both these patients possess other gene variants. Furthermore, we have found the Ser1342Gly variant in combination with other variants in four other nonrelated African American ER patients who are also CHCT positive.[36]

The presence of multiple rare *RYR1* variants or combinations of *RYR1* and *CACNA1S* variants is reported in a number of MHS studies with no further functional characterization of the findings.[37,38] In the case of cardiac RyR, the combined presence of two commonly occurring polymorphisms was associated with cardiomyopathy.[39] It is possible that the presence of multiple rare gene variants encoding amino acid substitutions in proteins essential for calcium regulation led to ER and MH in our patient. Further characterization of these genetic changes is required to determine whether they are pathogenic. It is also worth noting that the genetic screening methods used do not include untranslated regions, promoter regions, or epigenetic modifications, any

one of which alone or in combination may contribute to MHS.

Another topic worthy of consideration is the role that statin therapy may have played in exacerbating either ER or MH. Statins can be directly myotoxic, seem to trigger sustained increases in intracellular calcium, and are among the most commonly cited drugs for precipitating acquired rhabdomyolysis.[9] With prescriptions for the cholesterol-lowering statin agents increasing to an estimated 38 million in the United States by the end of 2008, statin-related rhabdomyolyis (SRR) may account for as many as 76,000 cases of rhabdomyolysis per year in the United States alone.[40]

SRR, defined as CK levels more than 10 times the upper limit of normal with muscle pain, tenderness, or weakness, has an incidence of 0.1–0.5%.[41] Furthermore, it has been shown that exercise in combination with lovastatin produced greater CK elevations than those produced by exercise alone, suggesting that statins can exacerbate exercise-induced skeletal muscle injury.[42] The adverse impact of statin therapy can be long lasting. Discontinuation of statin therapy does not guarantee recovery. At least 30% of patients with severe statin myopathy have exhibited symptoms for greater than 6 months, and some patients have exhibited symptoms for greater than 4 yr.[43] In fact, muscle biopsies from asymptomatic individuals taking statins show subclinical damage that includes breakdown of the T-tubular system and subsarcolemmal membrane rupture, but intact plasmalemma. Thus, CK does not leak from these cells into the circulation.[44] The exact mechanism of SRR is unknown but may be related to reduced levels of small proteins involved in myocyte maintenance.[45]

Genetic risk factors that may contribute to the development of SRR seem to be related to either drug metabolism or muscle metabolism. Candidate disorders of muscle metabolism that contribute to the risk of SRR, as well as ER, include inflammatory myopathies, mitochondrial myopathies, autosomal recessively inherited disorders of exercise intolerance, disorders of calcium homeostasis, and amyotrophic lateral sclerosis.[20,40] The negative Exercise Intolerance Mutation Panel and Myoglobinuria Evaluation tests eliminated some of the more common possible muscle disorders. MH falls into the category of disorders of calcium homeostasis. One case report and one case series evaluated patients with SRR for MH susceptibility using the IVCT.[46,47] In the case series, seven of nine patients had abnormal results, suggesting impaired calcium homeostasis and the possibility that latent MH susceptibility was unmasked by statin exposure. No genetic testing was performed, nor did any of the subjects report clinical episodes of MH during anesthesia.

On the basis of the history of ER, MH, positive CHCT and polymorphisms in three genes associated with skeletal muscle calcium regulation, this patient should not receive MH-triggering agents in the future. Although intravenous propofol infusions are popular as part of nontriggering anesthetics, rhabdomyolysis, metabolic acidosis, cardiac and renal failure (propofol infusion syndrome) can be adverse consequences of long-term propofol sedation, especially in pediatric intensive care unit patients.[48] While propofol may be contraindicated in other neuromuscular disorders, there is no evidence to suggest that propofol is unsafe in MHS patients.[49] This case illustrates how MH susceptibility is likely to have nonanesthesia-associated environmental and pharmacologic risk factors. Patients previously identified as MHS have been known to experience unexpected or recurrent heat and exercise intolerance.[50,51] These same symptoms, as well as SRR, may be diagnostic indicators of unrecognized MH susceptibility in others that require referral for MH testing.

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