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Trauma, Systemic Inflammatory Response Syndrome, Dietary Supplements, Illicit Steroid Use and a Questionable Malignant Hyperthermia Reaction

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Abstract

BACKGROUND—Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscle calcium regulation associated primarily, but not exclusively, with mutations in the skeletal muscle ryanodine receptor. Associated environmental factors, however, may also be important for expression of the syndrome.

METHODS AND RESULTS—A 24-yr-old trauma patient developed a fulminant MH crisis after a 3 minute exposure to sevoflurane. A thorough evaluation of underlying co-morbidities revealed a number of environmental factors that could have altered skeletal muscle calcium regulation, and may have potentially influenced the effects of volatile inhaled anesthetics. Since MH is a syndrome characterized by abnormal skeletal muscle calcium regulation, other factors that alter calcium homeostasis may exacerbate the impact of inhaled MH-triggering drugs.

CONCLUSIONS—While a thorough history of MH episodes in a proband and family is emphasized as part of a complete preanesthetic evaluation, obtaining a history of other environmental entities that may alter calcium regulation may be equally important to knowing the family history.

Malignant hyperthermia (MH) is a potentially fatal intraoperative syndrome characterized by “variable expression and penetrance.” Hence, individuals often do not develop clinical MH episodes with every exposure to anesthetic triggering drugs, nor is the temporal and clinical expression of the syndrome uniform. While it is part of routine preanesthetic evaluations to obtain a history of MH, it may be equally important to ask questions related to certain predisposing environmental factors that might make patients more likely to express the syndrome. This case illustrates how a combination of unusual environmental factors (trauma, systemic inflammatory response syndrome [SIRS], dietary supplements and the use of anabolic steroids) may have either alone or in combination altered the intracellular skeletal muscle milieu to induce or exacerbate a MH-like response.

CASE REPORT

A tracheally intubated, sedated 24-yr-old, 84-kg trauma patient presented for irrigation and debridement of his left groin wound 6 days after sustaining injuries. These included a left external iliac/femoral vein laceration, right pneumothorax, bilateral eye injuries, oral/dental

injuries, retroperitoneal hematoma, and numerous penetrating wounds to his trunk and extremities. By report, he was completely healthy before his trauma. He had undergone two previous uncomplicated general anesthetics with isoflurane (5 h total duration) in the last 6 days, after which he was placed on broad spectrum antibiotics for presumed ventilator-associated pneumonia and SIRS. In preparation for his third surgery, preanesthetic vital signs were: arterial blood pressure 159/63 mm Hg, heart rate 115 bpm, oxygen saturation 100%, and esophageal temperature 38.2°C. He was breathing spontaneously at 20 breaths per minute with pressure support of 8 cm H₂O, positive end-expiratory pressure of 5 cm H₂O, and fraction of inspired oxygen 50%. His pertinent chemistries were: hemoglobin/hematocrit 10.4/30.4, Na: 135, K:4.3, Cl:103, CO₂:31, glucose:81, blood urea nitrogen:4 Cr:1.1; arterial blood gases 7.45/40/154/27/99% (pH, Pco₂, Po₂, HCO₃⁻, SaO₂). IV fentanyl (250 µg), midazolam (2 mg), and vecuronium (10 mg) were administered. He was ventilated manually with 100% oxygen, and transferred to the main operating room. In the operating room, the anesthesia machine circuit was attached to the endotracheal tube, mechanical ventilation was initiated (minute ventilation of 7.5 L/min), and 2% sevoflurane was administered as the monitoring cables were transferred from the portable monitor to the anesthesia machine monitor.

Three minutes after the introduction of sevoflurane (2%), he developed tachycardia to 160 bpm, hypertension to 200/110 mm Hg, hyperthermia to 39°C, and end-tidal carbon dioxide (ETco₂) increased from 35 to 70 mm Hg, despite increasing minute ventilation up to 12 L/min. Minute ventilation could not be increased further due to decreased chest wall compliance and peak airway pressure of 40 cm H₂O. The arterial blood gases were 7.33/55/137/29/99% 7 min after initial sevoflurane exposure. A creatine kinase (CK) was ordered, as well as a baseline CK from blood drawn earlier that morning. Sevoflurane was discontinued 3 min after its initial delivery. Total IV anesthesia was initiated while hyperventilation with 100% oxygen, aggressive cooling and dantrolene (2.5 mg/kg IV bolus) were administered. After the dantrolene and external cooling, his temperature decreased to 38.1°C, heart rate decreased to 105 bpm, arterial blood pressure returned to baseline, and the ETco₂ decreased to 35 mm Hg without further changes in the minute ventilation.

The intraepisode CK was 11,750 U/L, an increase of 2136 U/L from a morning baseline of 9614 U/L. The surgery was postponed, and the patient received a total of 390 mg of dantrolene (210 mg initial loading bolus, plus 90 mg bolus 6 h later, and 90 mg bolus 12 h later) over 12 h. The CK values gradually declined, reaching 1470 U/L by postevent day 4. The family denied a history of MH and heat/exercise intolerance, but his mother reported that he gained 30 pounds of lean muscle mass by exercising and ingesting creatine monophosphate over the previous 6 mo. Upon recovery, the patient admitted to 6 mo of daily intense exercise, the ingestion of creatine monophosphate and Ripped Fuel® (Twinlab, NY, containing ephedrine, caffeine and aspirin), daily IM injections of the anabolic steroid deca-durabolin (nandrolone decanoate) and weekly testosterone. Five months after the clinical MH event and discontinuation of all muscle-building supplements (CK 97 U/L), he underwent a skeletal muscle biopsy with a Caffeine Halothane Contracture Test (CHCT). The CHCT was positive for MH susceptibility (MHS). Three separate muscle fascicles from the right vastus lateralis responded with contractures of 0.8, 1.6, and 1.5 g of tension, respectively, after exposure to 3% halothane, thus meeting the threshold criteria for a positive test, as defined by the North American Malignant Hyperthermia Group.¹ The responses to caffeine for three separate muscle fascicles were within normal limits. Standard muscle histology and histochemistry were normal. Screening of the entire ryanodine receptor type 1 gene (RYR1) and the α -1 subunit of the dihydropyridine receptor gene (DHPR), the only genes proven to be associated with MHS,^{2,3} was performed using RNA extracted from muscle. No RYR1 mutation or variant was found, nor any splice variant. Two DHPR polymorphisms (Leu458His and Arg1539Cys) were found. Both polymorphisms are reported in the public database (Single Nucleotide Polymorphism-SNP, National Center for Biotechnology Information). No DHPR α -1 subunit splice variant was found.

DISCUSSION

We describe an unexpected rapidly developing hypermetabolic event after a 3 minute exposure to sevoflurane, suggesting the diagnosis of MH. A score of 53 on the MH clinical grading scale⁴ places this patient in the highest probability category of “Almost Certain.” Furthermore, the CHCT was positive, though this would be considered an equivocal result by the criteria set forth by the European Malignant Hyperthermia Group since there was a response to halothane but not to caffeine. No novel or known pathogenic gene variants were found after screening the entire RYR1 gene and the α -1 subunit of the DHPR gene. There are at least three possible explanations for this discrepancy between phenotype and genotype: 1) this patient possesses an MHS-conferring mutation in another, yet to be identified, gene; 2) a false positive CHCT (78% specificity with 22% false positive rate⁵); and/or 3) a combination of environmental factors converged to alter intracellular calcium myocyte regulation in response to a volatile anesthetic and created an MH-like response.

While there may be other candidate genes, the RYR1 and DHPR genes are the only genes presently identified with MHS. With a specificity of 78%, we know that some non-MH myopathies will display CHCT positive results.^{6,7} Although there are no data or literature to support it, it is conceivable that pharmacologically altered muscle could also render a positive CHCT, making a MHS diagnosis factitious. Although the presence of a mutation in an unidentified gene may be the most plausible explanation, this cannot be proven nor can a factitious CHCT result be easily invoked. Thus, we will focus our discussion on the third possibility: that environmentally induced increases in intracellular calcium can contribute to the rapid evolution of a MH-like crisis.

Volatile inhaled anesthetics cause an increased release of calcium from skeletal muscle sarcoplasmic reticulum (SR) in both normal and MHS muscle; however, these drugs, have a greater impact on MHS muscle.^{8,9} This leads to cellular calcium overload, loss of cellular calcium control, and ultimately full-blown metabolic decompensation. Fulminant MH episodes result from a rapid, sustained increase in myoplasmic calcium,¹⁰ a phenomenon that has been shown repeatedly with halothane anesthesia.^{11–14} Since equimolar concentrations of sevoflurane are known to have a smaller impact than halothane in causing calcium release from the SR of normal skeletal muscle,¹⁵ and no mutation was found in the patient’s RYR1 or DHPR genes, the rapid MH onset observed in this case seems unusual. Since we do not know which genes were associated with this MH crisis, we cannot speculate on a genetic or protein mediated explanation for why sevoflurane produced such a rapid effect. We suggest, however, that environmental factors played a role in making sevoflurane such a potent trigger.

While it is not entirely clear what the combination of trauma, SIRS, dietary supplements, supraphysiologic doses of anabolic steroids, testosterone, and volatile anesthetics do to skeletal muscle myocyte calcium regulation, their individual contributions will be addressed. Both trauma and SIRS are hypermetabolic phenomena that can mimic MH, but it is unlikely that either participated in triggering this rapid MH crisis. Although the elevation in intracellular free calcium levels described in early sepsis and SIRS is blocked by dantrolene,^{16–18} classical SIRS is characterized by critical illness skeletal myopathy that results in impaired excitation-contraction coupling and weakness. It is often associated with myotoxic conditions that result in bioenergetic failure, mitochondrial dysfunction and inflammatory mediator-related proteolysis.¹⁹ None of the latter pathophysiological findings result in increased calcium availability from SR, and there is no evidence to suggest that SIRS enhances the calcium content in SR. SIRS/critical illness myopathy is more likely associated with conditions that result in muscle degeneration, making it leaky and causing increases in serum CK. Thus, the trauma and SIRS were likely causes for the continuing rhabdomyolysis. However, there is evidence that sepsis induces upregulation of RyR1 receptors in rat muscle,²⁰ suggesting that

more calcium channels are made available to the adverse calcium-releasing properties of the volatile anesthetics. Thus, MH might not have been induced by the abnormal quality of the RyR1, but by the increased quantity of the receptors. Moreover, one might argue that the concomitant trauma and SIRS compromised the normal cellular energetics necessary to maintain and regulate calcium homeostasis once the halogenated trigger was imposed.

Supraphysiologic doses of anabolic steroids (nandrolone decanoate) induce injury and apoptosis of differentiated skeletal muscle,²¹ and creatine dietary supplementation is associated with exercise-induced rhabdomyolysis.^{22–28} Again, while it is difficult to explain how these factors might have enhanced a MH trigger, it is tempting to speculate that compromised muscle loses the ability to mount homeostatic responses when challenged with MH triggers. Furthermore, two prior volatile general anesthetics over the period of 6 days could have also contributed to a subclinical, undetected influence on skeletal muscle calcium regulation. One possible explanation for the variable expression observed in MH is that uncompromised muscle is able to respond and maintain calcium homeostasis for some period of time when faced with a triggering agent. However, when the muscle is fragile via the mechanisms described, fulminant MH episodes might propagate much more rapidly.

Although the previously described environmental factors may have served only to weaken muscle, testosterone and Ripped Fuel possess actual calcium-releasing effects. Testosterone produces both genomic^{29,30} and nongenomic³¹ effects on skeletal muscle. The genomic effects involve interactions with intracellular androgen receptors which mediate gene expression,^{32, 33} whereas the nongenomic effects are characterized by a rapid second messenger mechanism, increasing the release of calcium from SR via inositol-1,4,5-triphosphate (IP₃) through phospholipase C activation in myotubes.^{31,34} However, there is no evidence that testosterone stimulation of IP₃ receptors in MHS muscle will induce MH, nor do we know how it might enhance myoplasmic calcium levels when given in combination with MH-triggering agents. Nevertheless, there is evidence that sevoflurane induces calcium release from a cholinergic cell line (SN56) via an IP₃ mechanism,³⁵ and there is evidence that the skeletal muscle of MHS patients contains higher levels of IP₃ than do normal patients.³⁶ These data suggest a possible role for testosterone-mediated augmentation of calcium release via an IP₃ mechanism in association with sevoflurane in MHS muscle.

Ripped Fuel is a stack weight loss product that contains high concentrations of ephedrine, caffeine and aspirin, which sensitizes the RyR1 to calcium release and has a separate thermogenic effect.^{37,38} Caffeine directly binds to the RyR1, inducing calcium release, and could have potentially sensitized the RyR1 to the effects of sevoflurane. However, our patient had not consumed Ripped Fuel for at least 6 days before his MH event and no mutation was found in his RYR1 gene. What role caffeine played is unclear, as this explanation would suggest that any person consuming Ripped Fuel might become sensitized to volatile anesthetics and respond as if they had MH. It should be noted that genetic screening was performed using RNA extracted from muscle, converted to cDNA and followed by polymerase chain reaction. The advantage to using RNA is that not only are genetic variants in the coding regions of the DNA identified, but it also captures possible aberrant splicing in the noncoding regions that could lead to the formation of nonstandard protein subunits.

A major conceptual issue that needs to be addressed is how, in the absence of genetic changes in the RYR1 and DHPR, prolonged pharmacological abuse sensitized muscle to the MH-causing effects of volatile anesthetics. After removing the offending drugs and return to normality by CK criteria, the patient's muscle still had an abnormal response to halothane in the CHCT. It is assumed that the effects of drugs disappear with their disappearance. However, prolonged abuse of other drugs in many other receptor systems alters the quantity of receptors expressed. The problem might not be with expression of an aberrant gene, but the level of

expression of a normal gene that codes for a receptor known to cause increased calcium release with exposure to volatile anesthetics. Thus, normal genes might cause MH if they are expressed under the right circumstances. It would be interesting to repeat the live muscle biopsy and CHCT in this patient to see if there is extinction of the MH sensitivity.

It has been suggested that a twofold increase of the resting myoplasmic calcium concentration is the critical threshold, sufficient and necessary, to initiate a halothane-mediated MH episode in the homozygous MHS swine,³⁹ but higher concentrations are needed to induce a full-blown hypermetabolic response.⁴⁰ We know that MH-triggering drugs enhance the release of calcium from the SR, but what may ultimately be critical is the myoplasmic calcium concentration. Factors that augment resting myoplasmic calcium may enhance the speed of onset of a MH crisis. While we do not know what our patient's resting myoplasmic calcium concentrations were, both at rest and before sevoflurane exposure, it seems conceivable that his pre-sevoflurane levels might have been elevated.

When addressed individually, arguments can be made for how each environmental factor may or may not have played a role in the observed MH-like crisis, but it is likely that each played a role in influencing skeletal muscle metabolism. What is not known is how each factor influences the others when presented in combination on the background of an unknown MH gene mutation, or, if no mutation is present, whether such pharmacological abuse alone is capable of inducing an MH-like reaction. Unfortunately, these complex events make it difficult to provide concrete clinical recommendations. However, clinicians should be alerted that events and drugs that alter normal skeletal muscle calcium metabolism may impact the safe administration of volatile anesthetics.

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