The Relationship Between Exertional Heat Illness, Exertional Rhabdomyolysis, and Malignant Hyperthermia

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Exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia (MH) are complex syndromes with similar pathophysiology. All three are hypermetabolic states that include high demand for adenosine triphosphate, accelerated oxidative, chemical, and mechanical stress of muscle, and uncontrolled increase in intracellular calcium. Although there are no controlled clinical studies to support a relationship, there is evidence to suggest an association between unexpected heat/exercise intolerance and MH susceptibility. There are multiple case reports and a small number of clinical studies that have used *in vitro* muscle contracture testing and/or genetic testing to make the association. However, such methodology is problematic in that these tests are validated for clinical MH in association with anesthesia, and not for exertional heat illness or exertional rhabdomyolysis. Nevertheless, these relationships may have implications for some MH-susceptible patients and their capacity to exercise, as well as for clinicians treating and anesthetizing patients with histories of unexplained exertional heat and exercise illnesses.

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Exertional heat illness (EHI) and exertional rhabdomyolysis (ER) are complex syndromes with diverse etiologies that plague military recruits in basic training, physically fit well-conditioned athletes, and the physicians called upon to treat them. It is clear that under extreme physical and environmental conditions anyone may develop a heat or exercise-related illness.[1] Less clear is who is predisposed, who will develop sequelae, and who will have recurrence. It is not surprising when EHI or ER occurs in poorly conditioned, unacclimated individuals performing extreme physical activity sometimes under extreme environmental conditions. What is more vexing are the sudden and unexplained cases that occur in the physically fit, well conditioned and acclimated who have been exercising their entire lives without previous problems. 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 EHI/ER and malignant hyperthermia (MH).[2]

Typically, MH is an inherited subclinical myopathy characterized by a hypermetabolic reaction during anesthesia. This reaction is related to skeletal muscle calcium dysregulation triggered by volatile inhaled anesthetics and/or succinylcholine. Manifestations of a MH crisis can include skeletal muscle rigidity, mixed metabolic/respiratory acidosis, tachycardia, hyperpyrexia, rhabdomyolysis, hyperkalemia, elevated serum creatine kinase (CK), multiorgan failure, disseminated intravascular coagulation, and death.[3] Individuals are labeled as MH susceptible (MHS) if they have a well-documented clinical episode consistent with MH during exposure to any of the known triggering agents, or if they have undergone a skeletal muscle biopsy with a positive diagnostic contracture test.

EHI is a disorder of excessive heat production, coupled with insufficient heat dissipation. It typically occurs in the summer in unacclimated individuals who overexert themselves in hot/humid environments, causing a dangerous increase in the body's core temperature. EHI can progress to exertional heat stroke (EHS), which includes central nervous system abnormalities coupled with extreme hyperthermia (core body temperature higher than 40°C or 104°F). EHS can cause critical injury to all organ systems, including thermoregulatory, renal, cardiovascular, musculoskeletal, and hepatic.[2,4] ER is a frequent complication of EHI, but can occur in the absence of high environmental or core body temperatures. ER is a syndrome of diverse etiology that can occur in response to strenuous exercise when mechanical and/or metabolic stress damages skeletal muscle, causing elevated serum CK and potentially leading to hyperkalemia, myoglobinuria, and renal failure.[5] The criteria for ER are somewhat controversial, but clinical practice guidelines recognize muscle pain and fatigue coupled

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with serum CK level ≥5 times the upper limit of normal as diagnostic.[5]

Rhabdomyolysis is classified as either inherited or acquired. Although metabolic myopathies are not the most common etiology for EHI or ER, they should be carefully considered in patients who have recurrent episodes that are triggered by low levels of stress or exertion.[1] The final common pathway for all cases of rhabdomyolysis is destruction of muscle cells as a result of direct or indirect injury with displacement of their intracellular contents into the extracellular fluid, the circulation or both. Shared features of MH, EHI, and ER are hypermetabolic states that include a high demand for adenosine triphosphate, accelerated oxidative, chemical, and mechanical stress of muscle, and an uncontrolled increase in intracellular calcium. These processes overwhelm the normal cellular regulatory mechanisms and severe muscle injury and death occur in certain individuals. These similarities have raised the possibility that EHI, ER, and MH are related syndromes triggered by different mechanisms.

Although MH is a pharmacogenetic disorder, nonpharmacologic environmental factors may trigger clinical manifestations without exposure to the classical anesthesia triggering agents. In 2001, Tobin et al. reported the case of a 12-yr-old who was labeled MHS by clinical episode, but had not undergone a caffeine halothane contracture test (CHCT, the validated diagnostic laboratory test for MHS). The patient developed EHS and died after playing football in mild weather.[6] Postmortem genetic analysis confirmed the presence of a known MH-associated mutation in the ryanodine receptor Type 1 gene (*RYR1*), the gene most strongly associated with MHS.[7] Furthermore, the child's father was also found to have the same mutation. What follows is a literature review discussing the association between EHI/ER and MH, and the possibility that some EHI and ER patients may be genetically predisposed to injury due to MH susceptibility.

THE EHI AND MH RELATIONSHIP

Although the Tobin et al. case is an example of a known MHS individual developing fatal EHS, investigators had long suspected that some EHI patients might have undiagnosed MH susceptibility. In fact, the idea that stress or exercise-induced awake episodes of MH similar to that seen in porcine stress syndrome was suggested by several publications 20–30 yr before the Tobin et al. case.[8–14] In 1983, Campbell et al. measured various physiologic variables in response to exercise in documented MHS subjects versus controls. They found that MHS subjects developed higher central temperatures and that thumb and chest wall temperature increased more slowly. This suggested that heat dissipation in the periphery was diminished as central temperature increased. Furthermore, MHS subjects maintained higher cortisol, free fatty acid, and lactate levels.[15] However, none of the subjects developed EHI or ER. In an exercise study of MHS subjects by Green et al.[16], thermoregulatory, plasma catecholamine, and metabolic responses were no different from controls. Thus, the few exercise studies that have been performed in MHS subjects have not provided clear answers regarding the risks of exercise.

In 1991, Hackl et al. performed the *in vitro* contracture test (IVCT, the European equivalent of the CHCT) on two patients who developed fever and severe myolysis during exercise. One was confirmed MHS, but no *RYR1* genetic testing was performed.[17] That same year, two soldiers who collapsed with EHS underwent IVCT and were found to be MH equivocal (positive to halothane, negative to caffeine). The father of one soldier was also positive to halothane, and muscle from the father of the second soldier had an abnormally strong response to ryanodine.[18] In another study from 1993, 19 of 45 EHS patients were diagnosed MHS by IVCT.[19] In 1996 and 1998, two more case reports linked episodes of EHI to positive CHCT or IVCT.[20,21] Both of these patients presented with muscle complaints and hyperthermia after exercise in hot, humid climates. Finally, a study from 2001 reported 26 of 250 EHS survivors with abnormal IVCT and abnormal muscle energetics as measured by ^{31}P-magnetic resonance spectroscopy.[22] Unfortunately, none of these studies performed *RYR1* genetic testing.

Other than the Tobin et al. case, there is only one other published case that links a previously known positive family history of MH to an EHS death in a family member.[23] However, there is an unpublished case from the MH Testing Center at the Uniformed Services University of the Health Sciences of an individual with a clinical episode of MH and positive CHCT, who 5 yr after his MH episode experienced two episodes of EHI (one classified as EHS) under high heat and humidity. This individual's father was also found to be CHCT positive.

Subsequently, this patient also developed two episodes of ER without hyperthermia while exercising in a moderate climate. CK measurements exceeded 160,000 IU. This individual had sought careers in both the armed forces and law enforcement, but was disqualified for both due to his repeated episodes of EHI, ER, and MHS. Unfortunately, genetic testing has not been performed.

THE ER AND MH RELATIONSHIP

The relationship between unexplained ER and MHS was reported in 1991 when Poels et al.[24] performed IVCT on six patients with nonanesthesia-induced rhabdomyolysis, two of whom had ER. Five of the six patients were IVCT positive, one of whom had ER. In a later study, 49 neurologically asymptomatic patients with persistently elevated CK underwent CHCT. Twenty-four of 49 (49%) were CHCT positive.[25] However, the most compelling study linking

ER to MHS was published by Wappler et al. in 2001. They performed the IVCT on 12 unrelated ER patients without family or personal histories of MH. Ten of 12 were found to be MHS, and 1 of 12 to be MHE. Unlike previous studies, a limited genetic screen was performed, revealing three *RYR1* causative mutations among the 10 MHS subjects.[26] Finally, in 2002, Davis et al.[27] published a report of two unrelated ER patients without histories of MH, who were both CHCT positive and shared a common *RYR1* variant.

There is only one documented case in which suspected MH occurred first followed by a history suspicious for repeated ER.[28] At age of 6 yr, the patient developed masseter muscle rigidity and CK of 5362 IU on induction of anesthesia. Over a 3-yr period between age 12 and 15 yr, this child is reported to have experienced up to 100 episodes of generalized body rigidity, dyspnea, and painful calf spasms. A CHCT performed at age of 18 yr was positive, and genetic analysis revealed a *RYR1* variant.

RECOMMENDED GUIDELINES FOR EHI/ER WORK-UP

The differential diagnoses for EHI and ER are extensive. Thus, the most obvious and common causes should be addressed before considering a MHS evaluation. Treatment should focus on rapid cooling, aggressive hydration for renal preservation, and electrolyte correction. The majority of EHI and ER are not related to MHS, and MHS is only one of many possible inherited causes (glycolytic/glycogenolytic, fatty acid oxidation, Krebs cycle, pentose phosphate pathway, purine nucleotide cycle, mitochondrial respiratory chain).[1] There is no published algorithm to evaluate recurrent or unexpected EHI and ER. What follows are recommendations based on United States Army Regulation 40-501 and a military supported "Clinical Practice Guidelines for Exertional Rhabdomyolysis" document in preparation at the Uniformed Services University of the Health Sciences. A team of military sports medicine specialists, physiologists, neurologists, pathologists, geneticists, and anesthesiologists have developed this approach, but only future research will determine if these guidelines are justified.

Evaluation of unexplained or recurrent EHI or ER, with or without sequelae, begins with a complete neurological evaluation to include physical examination, electromyogram, serial CKs, myoglobin, urinalysis, standard electrolytes and chemistries, lipid panel, thyroid panel, metanephrine panel, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, rapid plasma reagin, human immunodeficiency virus, and an exercise intolerance panel. Specifically, the Exercise Intolerance Mutation Profile (The Robert Guthrie Biochemical Genetics Laboratory, Buffalo, NY) is a DNA blood test that screens for the most common mutations in the *CPT2*, *PYGM*, and *AMPD1* genes, which code for the enzymes carnitine palmitoyltransferase 2, myophosphorylase, and myoadenylate deaminase, respectively.[29]

If the above evaluation is nondiagnostic and the neurologists request an open muscle biopsy for standard histopathology and histochemistry, a CHCT is performed at the same time. If the CHCT is positive, *RYR1* genotyping is performed. At the time of muscle biopsy, another 250 mg of muscle is frozen and sent for a Myoglobinuria Test Panel (The Robert Guthrie Biochemical Genetics Laboratory, Buffalo, NY or Athena Diagnostics, Worcester, MA). This panel is an enzymatic screen to test for phosphofructokinase deficiency, McArdle's disease, Tarui's disease, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency, glycogen, phosphorylase A+ total deficiency, phosphorylase B kinase deficiency, carnitine palmitoyltransferase 2 deficiency, and myoadenylate deaminase deficiency.[29]

CONCLUSIONS

The problem with this literature review is that the CHCT and IVCT are tests validated for clinical MH, and not for EHI or ER. Thus, using the CHCT and IVCT to label EHI and ER patients as MHS is questionable. Furthermore, with a sensitivity of 97% and specificity of 78%,[30] the CHCT was purposely designed to minimize false negatives to avoid the risks of MH crises. This potentially results in the overdiagnoses of MHS. With a false positive rate of 22%, the CHCT is diagnosing some normal patients as MHS and capturing some non-MHS related myopathies.[31,32] Nevertheless, the predictive value of a diagnostic test is more important to the clinician than the sensitivity or specificity, and the CHCT has an excellent negative predictive value.[33] The IVCT for diagnosis of MHS in Europe has a 99% sensitivity and 93.6% specificity.[34]

Although there is evidence to suggest that some individuals with histories of clinical MH and positive CHCT or IVCT may develop heat or exercise intolerance, there is no evidence for the converse. In fact, none of the reported cases of patients who first presented with EHI or ER and who were subsequently diagnosed as MHS by positive CHCT or IVCT had documented clinical MH episodes involving anesthesia. Although some EHI and ER patients may be MHS by contracture testing, this does not mean that a causal relationship is proven. Further clinical and basic science studies are needed.

There are many inherited and environmental factors that can contribute to EHI and ER, one of which is MHS, but there is not much evidence to reliably predict what percentage of EHI and ER is related to MHS. Support for an association between EHI and MH is evidenced by recent studies in mice with a MH mutation (Y522S) in the ryanodine receptor that showed muscle contractures, rhabdomyolysis, and death in response to elevated environmental temperatures.[35] Although this study is positive, it represents

only one *RYR1* mutation in a nonhuman model. Moreover, the same mouse model did not develop rhabdomyolysis when muscle was subjected to repeated bouts of eccentric contractions when core temperature was maintained at lower physiological temperatures during exercise.[36]

There is a link between EHI/ER and MHS, but controlled functional exercise studies are needed to establish the true risks. Some patients with EHI and ER will be CHCT or IVCT positive, and some of those patients will have *RYR1* variants. However, 205 *RYR1* variants have been identified, of which only 29 have been functionally characterized to be causative for MH. (The total number of variants was updated and submitted to the Gene Test website [http://www.genetests.org] in 2008, Nyamkhishig Sambuughin personal communication; there are 29 functionally characterized mutations according to the European Malignant Hyperthermia Group website [http://emgh.org]) Thus, an *RYR1* variant must be proven causative before it can be considered indicative of MHS, even in association with a positive contracture test. Moreover, a negative *RYR1* screen with a positive contracture test does not necessarily mean that the patient is not MHS, as there are likely yet unidentified non-*RYR1* mutations that confer MHS.

In 2002, Grogan and Hopkins[37] suggested that all individuals with histories of EHS or allied symptoms be referred for MHS screening. Although this approach would be very useful for a better understanding of the relationship between EHI and MHS, it would also be quite costly. Unfortunately, there is still not much evidence to provide concrete recommendations to clinicians on how and if they should alter their anesthetic plans in patients with histories of EHI and ER. Perhaps it would be useful to publish a survey of European and North American MH experts on how they would anesthetize such patients. It may be advisable to provide non-MH triggering anesthesia to patients with unexplained EHI or ER until definitive diagnostic muscle contracture testing can be performed. Although the evidence for a relationship among EHI, ER, and MH is compelling, further research is needed.

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