Original Article

Association of malignant hyperthermia and exertional heat illness in young athletes: An analysis of awareness among clinical and athletic first responders

ABSTRACT

Background: Malignant hyperthermia (MH), a rare inherited condition seen almost exclusively in the perioperative setting, is triggered by volatile anesthetics or an intravenous paralytic drug, succinylcholine. It can, however, occur without any exposure to anesthetic drugs, being associated with heat illness and rhabdomyolysis, thus presenting a little-known risk to young athletes exercising in hot environments.

Objective: This study aimed to determine the first responder awareness of MH and its association with heat illness in young athletes within athletic and clinical environments.

Methods: Awareness within the clinical milieu was assessed by an institutional chart review of 3296 charts. The identified heat illness cases were examined for treatment consistent with the management of a suspected episode of MH. Awareness among first responders in an athletic setting was examined by a survey administered to a total of 1,500 coaches and athletic trainers at the high school level along with emergency medical services providers across the United States.

Results: No treatment consistent with the suspicion of MH was noted among clinical first responders, suggesting a lack of awareness. Survey administration also revealed a limited amount of knowledge of MH and its potential role in heat illness.

Conclusion: The results point to lack of awareness among pre-hospital and hospital-based first responders of the relationship between MH and heat illness in young athletes. An effort to educate these members of the healthcare community can contribute to an expeditious and life-saving intervention.

Clinical Relevance: First responders who may interact with a young athlete have low knowledge of MH and its relationship to heat illness. Similar lack of awareness exists among hospital personnel who care for young individuals with heat illness. Educating the first responders about this condition can speed up the time to intervene and save lives.

Key words: Anesthesia, athletic training, injury prevention, medical aspects of sports, muscle physiology, pain management, pediatric sports medicine

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Stacey Watt, James Chue[1], Remek Kocz

Department of Anesthesiology, University at Buffalo, Buffalo, NY, USA, [1]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

Address for correspondence: Dr. Remek Kocz, Department of Anesthesiology, University at Buffalo, Buffalo, NY, USA.
E-mail: rkocz@buffalo.edu

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Introduction

Malignant hyperthermia (MH) is a severe pharmacogenetic disorder of skeletal muscle manifested by a hypermetabolic response with exposure to certain potent volatile anesthetics or the depolarizing neuromuscular blocking drug succinylcholine. It is caused by the dysregulation of calcium homeostasis within the muscle cell. MH is a condition inherited in an autosomal dominant fashion, and it is usually thought of as being limited in its scope to the perioperative environment. Thus, anesthesiologists and critical care practitioners are the only individuals who may have an opportunity to ever diagnose and treat it.

Malignant hyperthermia susceptibility (MHS) can be diagnosed via an *in vitro* caffeine-halothane contracture test (CHCT) by measuring *in vitro* contractile responses of freshly excised skeletal muscle exposed to halothane or caffeine. Alternately, MHS can be diagnosed based on a mutation in the RYR1 gene for the ryanodine receptor of skeletal muscle, the first and most common genetic predisposition described. However, this mutation is often not present in MH cases due to locus and allele heterogeneity.[1-3] Alternatively, CACNA1s or STAC3 genes are also associated with MH. Patients susceptible to the condition have subclinical physiological differences in their muscle tissue. Their muscle tissue has been shown to respond to short-duration, high-intensity exercise with a larger decrease in pH and longer time to recovery than control.[4,5]

Most heat illness occurs in young, healthy patients during exercise, often in hot or humid climates without appropriate acclimatization, often secondary to heat gain from the environment. Other factors such as obesity, lack of physical fitness, sweating disorders, viral illnesses, alcohol consumption, or medication use can contribute. There are, however, individuals without any predisposing factors who develop an exertional heat illness (EHI) and are the only sporadic cases out of possibly thousands of other participants. This situation raises suspicion of a rare underlying genetic predisposition. Several reports have revealed that some patients with a history of EHI have fulfilled the criteria for MHS by diagnostic laboratory testing. Similarly, testing of first-degree relatives also revealed at least one parent with MHS, suggesting a genetic susceptibility in certain individuals. As many as 30% of patients with EHI have a variant of the RYR1 gene.[1]

Over several decades, there have been troubling reports of what appeared to be MH reactions without triggering anesthetic drugs.[6] These reports have involved young adults exercising vigorously in a warm environment, suddenly having an awake episode resembling MH, characterized by hyperthermia, diaphoresis, tachypnea, tachycardia, muscle rigidity along with laboratory findings of acidosis, hyperkalemia, and rhabdomyolysis. These episodes have often resulted in death. Unlike the closely monitored environment within an operating room, with anesthesia personnel prepared to recognize the early signs and symptoms of MH, these individuals were not monitored. Thus, the physiologic abnormalities are randomly observed and poorly documented. There is often significant time to recognize an episode by untrained individuals, meaning medical help is often sought late, and it may not be until the hospital setting where they receive appropriate care.[7] These potentially fatal episodes are rare and present with nonspecific symptoms ranging from hyperthermia, muscle cramps, exertional pain, and rhabdomyolysis to a life-threatening hypermetabolic reaction in physically fit and seemingly healthy individuals without a personal or family history or MH, which makes diagnosis challenging even for trained professionals.[8]

Young athletes suffering such reactions depend upon coaches, trainers, and emergency medical services (EMS) personnel to identify their symptoms and act appropriately until they can be cared for by more specialized providers in a hospital setting. When a high school athlete suffers heat illness symptoms, the differential diagnosis formed by his or her first responders is unlikely to include an awake MH episode, and this failure in diagnosis and the subsequent delay in treatment can result in a fatality.[9,10]

The goal of this study was to assess the knowledge and awareness of MH within both a clinical setting and among athletic professionals who would act as first responders in an event of a young athlete experiencing an episode of heat illness.

Methods

An Institutional Review Board (IRB) exemption was applied for and subsequently was granted to conduct this research. Two methods of assessment of MH awareness were used, depending on which population was studied. Hospital-based awareness was assessed by the response analyzed in a chart review, and the first responder awareness was assessed via a survey.

Chart review

A retrospective review of 3,296 patient records containing International Classification of Diseases, Ninth Revision (ICD-9) codes corresponding to fever (780.6), heat stroke (922.0), and heat exhaustion (992.5) was undertaken. The review was

conducted by two attending anesthesiologists, the authors Kocz and Watt, utilizing the electronic health record (EHR) data from the Women's and Children's Hospital located in Buffalo, New York. Because our interest was in young athletes, we looked to include an age range that would include children from early grade school through the final year of high school. Children in that age range would be very likely to participate in recreational or organized sports. We thus selected individuals 8 to 18 years old who presented to the emergency department with temperatures 39.9°C or greater during the 2-year period encompassing 2014 and 2015. The resulting 17 charts [see Table 1] were reviewed for notes, orders, and clinical treatment courses that would have suggested a workup that included suspicion of an awake MH episode.

Survey

Utilizing the SurveyMonkey online tool, a 16-question survey was distributed to the three first responder groups. The questions, listed in the Appendix, assessed the basic demographics and the level of awareness of the relationship between heat illness and MH.

The survey was sent to 1,500 US first responders comprised of 500 high school athletic coaches or coach assistants, 500 high school athletic trainers, and 500 EMS personnel. Three professional associations distributed the survey links. Each association was sent an email describing the research study, a consent statement, and a link to the survey. The survey questions are listed in the Appendix.

Patient involvement

No patients or the public were involved in the design of the study, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on the interpretation or writeup of the results.

Table 1: Patient characteristics from chart review. Cases presenting with fever exceeding 39.9°C

Patient characteristics	(*n*=17) Mean±SD
Age	11±3.3
Gender-female	6 (35%)
Gender-male	11 (65%)
Weight (kg)	47.5±19.9
Height (cm)	149±21
BMI	21.2±5.3
Admission temperature (Celsius)	40.3±0.3
Admission BP (mmHg)	112/66±9/7
Admission HR (BPM)	123±15
Discharge temperature (Celsius)	37.9±1.0
Discharge BP (mmHg)	105/61±12/10
Discharge HR (BPM)	111±21

Results

A total of 17 cases were identified from the EHR chart review. Refer to Table 1 for admission and discharge characteristics. Of the total, 11 were treated for nonspecific fever. Antipyretics, along with a fluid bolus, were the most frequent treatments administered. Occasionally, an anti-emetic and/or nonsteroidal anti-inflammatory drug (NSAID) were also given. Basic laboratories were obtained, such as complete blood count, basic metabolic panel, and short biochemical panel (Chem-7). By the time a physician examined these children, in several, their fever had already subsided. In every patient, the vital sign derangement was resolved by the time they were discharged. In one of the cases, there was exercise-induced hyperthermia in a 7-year-old female in the ER. Although a physician saw her, no further laboratory investigation was performed. Thus, during the episodes of heat illness in the community among young, exercising children, no clinical approaches toward diagnosing an awake episode of MH were undertaken.

Our survey administered to first responders who would likely be involved in the pre-hospital care of a young athlete pointed to inadequate knowledge of MH. Of all respondents, 62.4% reported that they did not know what MH is. The most pronounced knowledge deficit was noted in the coaches or coach assistants (75.8% unfamiliar), with better scores in athletic trainers (53.4%) and EMS providers (58.1%), as visualized in Figure 1. More significantly, an overwhelming majority of these respondents (73.1%) were unable to correctly identify the nature of MH, cumulatively. Most pronouncedly, only 15.2% of coaches or coach assistants pointed to MH as a skeletal muscle disease. Athletic trainers and EMS providers were expected to outperform the coaches, and indeed, they achieved identical results in their tally of correct answers (33.1% and 32.8%, respectively), as shown in Figure 2. Finally, almost 74% did not know dantrolene, the muscle relaxant, which is the primary treatment for MH. As Figure 3 illustrates, all the groups were similarly unaware of the drug and its role in the treatment of MH.

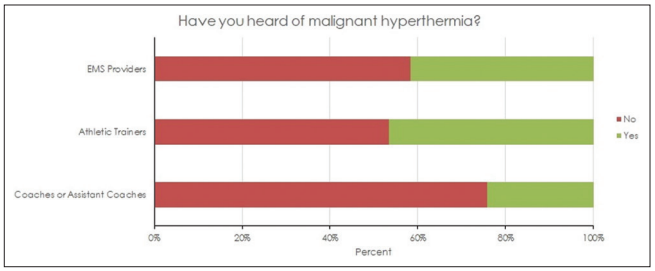

Figure 1: Results of survey answers to the question "Have you heard of malignant hyperthermia?"

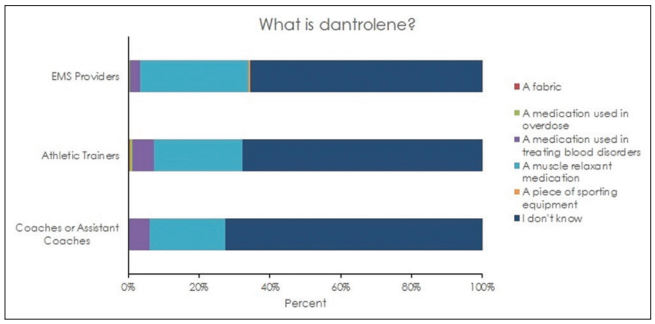

Figure 2: Results of survey answers to the question "What is malignant hyperthermia?"

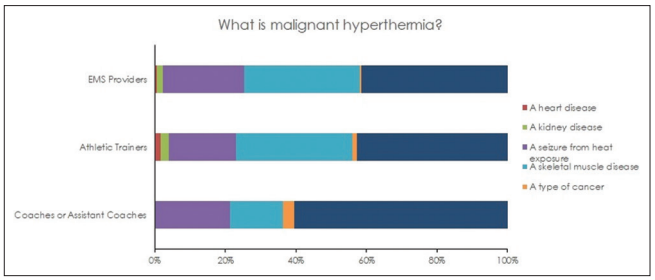

Figure 3: Results of survey answers to the question "What is dantrolene?"

Discussion

Heat-related illnesses are rare in the general population, with an average rate of 21.5 visits/100,000 population/year, and as their subset, MH is even rarer, with the prevalence of MH approximately 1 per 100,000 surgical discharges.[11,12] The North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States has only 291 recorded cases.[13] The Registry has been collecting data on MH since 1987, allowing for submission of information from both the patients and the physicians. The highest awareness of MH is among anesthesiologists, whose training places significant focus on diagnosis, treatment, and prevention of the condition. The rare nature of awake MH episodes suggests that the physician treating the individual is unlikely to be an anesthesiologist. As our research has borne out, awareness among non-OR providers and the athletic community is much lower. Considering the resources invested in MH prevention and treatment, educational intervention for personnel involved in pre-hospital care of heat-related illness, such as coaches, trainers, and EMTs, could be used as a cost-effective tool to improve knowledge, recognition, treatment, and outcomes.

Although certain genetic mutations are more commonly involved in MH, many different genes or mutations can lead to the condition. Some have been identified, but not all MH or MHS can be explained by these. Theoretically, any mutation that leads to dysfunction of calcium regulation in the cell could predispose to MH and heat-related illness. Due to the rarity of the condition, it is not easy to test and analyze. The *in vitro* contracture test (IVCT) of muscle is an invasive and expensive test requiring a surgical procedure to obtain a muscle biopsy.[2] It is recommended that muscle biopsy and an IVCT should be performed in all patients with severe clinical episodes resembling exercise-induced MH.[14] Our record review from the EHR charts suggested low awareness for patients with high fevers of at least 39.9°C. Providers treated their fever but did not investigate a cause once resolution occurred. There was also a lack of follow-up.

Considering that higher rates of MHS have been suggested in patients who suffered EHS, those who could potentially be identified as at risk for MHS were not counseled or investigated further. Clearly, it would be of utmost importance to warn these individuals of the dangers of MH. Disease rarity, poor diagnostic approaches and workup, invasive and expensive testing, and resulting paucity of information about awake MH episodes all result in a lack of knowledge about the disease in athletic, first responder, and medical community.

Heat-related illness is inherent to physical activity, and its incidence increases with effort, heat, and humidity. Susceptible individuals with diagnosis determined by CHCT or molecular genetic testing of pathogenic variants in CACNA1S, RYR1, or STAC3 genes, however, are more likely to be affected. Understanding these predispositions can help better prevent and treat these individuals.[15-17]

Both EHI and MH are deadly diseases. The trigger mechanisms for the two diseases are different, but both lead to cellular energy depletion, acidosis, calcium accumulation, and excess heat production. Organ dysfunction and subsequent failure can result, especially with core temperatures exceeding 40°C. Many MH and MH-susceptible cases involved RYR1 gene abnormalities, but only some EHI cases did. Dantrolene is effective in some EHI cases, but is a proven treatment in MH or MHS. Any patient with personal or family history of MH or MHS and presenting with a heat illness should be given dantrolene.[1]

Theoretically, dantrolene can treat any condition where excessive muscle heat production is the cause of hyperthermia, including MH and EHI but not classical heat stroke, in which the heat is gained from the environment. It has been suggested that dantrolene be used in EHS patients with severe features, such as temperature >39°C, despite aggressive fluid resuscitation, cooling, and overt muscle rigidity unrelated to hyperkalemia or seizures.[1,18]

Physical stress can trigger porcine models of MHS to MH without exposure to triggering anesthetics. It was thought that this did not occur with humans. However, there are several troubling case reports from the literature. In the

1970s, a patient presenting to the Mayo Clinic reported that after emotional or physical stress, he developed fevers >40°C resistant to aspirin and cooling that spontaneously broke after a few days. His treatment included oral dantrolene, which resolved his symptoms rapidly during these events. When genetic testing was later available, he was found to have an AMPD1 mutation suggestive of myoadenylate deaminase deficiency, a muscle disorder in which the MH susceptibility is unclear.[7,18]

Another case report involves a child, age 12, who underwent general anesthesia with sevoflurane for a fracture. Fifteen minutes later, the patient had an abrupt increase in end-tidal CO_2 (>70 mmHg), HR >150, with a temperature of 39.4°C. He was diaphoretic but not rigid and treated with dantrolene. Following this event, he recovered without sequelae. Eight months later, the patient played football at an ambient temperature of 26°C. Following the game, he complained of weakness. Pre-hospital personnel found him hot, diaphoretic, hyperventilating, and complaining of tingling. These symptoms progressed to seizure with respiratory arrest. EKG revealed sinus tachycardia, and intubation was unsuccessful due to jaw rigidity. Ventricular fibrillation began, and ACLS started. Upon arrival at the hospital, the patient was successfully intubated. Dantrolene treatment was instituted. Despite treatment, his rectal temperature was 42.2°C, and his potassium rose to 14.5 mEq/L. The resuscitation was ultimately unsuccessful after 1 hour. No muscle biopsy for the purposes of CHCT was taken due to premature death. Postmortem analysis was largely unremarkable. The family tested positive for RYR1 gene mutation. Given this example, it is easy to see that an awake MH episode may be mistaken for heat stroke that is unsuccessfully treated.[19]

A 7-month-old male baby had an MH reaction to halothane anesthetic but recovered after treatment. From 20 months onwards, he had multiple non-anesthetic MH-like events, including fevers, tachycardia, rigidity, elevated creatine kinase, and hyperkalemia in response to high environmental temperatures, underlying illnesses, and spontaneously. At age 5, contraction testing to caffeine/halothane from a muscle biopsy was significant for MHS. These episodes responded to cooling and dantrolene, but he died en route to the hospital during one of the episodes. Lastly, a 6-year-old girl with a history of spontaneous MH-like symptoms was hospitalized for rigidity and fever up to 42.2°C and passed away despite dantrolene, cooling, and cardiopulmonary resuscitation. Both patients had an R3983C mutation on the RYR1 gene, which has been found to modestly potentiate caffeine-induced Ca^{2+} release *in vitro*.[20]

A study of 454 patients from the French Armed Forces who suffered an EHS episode found an unexpectedly high prevalence of MHS. Using IVCT, 45.6% of cases were found to be diagnostic, with 17.2% positive for both caffeine and halothane, a much higher frequency than the approximately 0.03–0.05% in the general French population. However, the study is not conclusive for several reasons. Patients were tested following an EHS episode, meaning causality cannot be established. There are also very few case reports in the literature of EHS following MH. Finally, IVCT is not specific to MH and can be positive in other diseases, such as Duchenne's muscular dystrophy.[21]

In 2015, the National Athletic Trainers' Association published a position statement on EHI. Several heat-associated illnesses have been defined, including heat syncope, exertional heat exhaustion, exertional heat stroke, and heat injury. These conditions are a spectrum of the same disease process whereby heat gain arises from an interaction between the environment and exertional heat generation, unlike MH, which is primarily metabolic. Although different, there is still significant relevance to MH as many aspects of care are similar. To healthcare providers and first responders, the best results are achieved in early recognition and treatment that consists of aggressive cooling to average temperature. As noted in the position statement, avoiding the same-day return to activity in persons suffering from heat illness is strongly recommended. Delayed treatment can lead to residual complications for months to years but many recover in less time. Regardless, these individuals should be restricted in the type of activity performed, and a plan of gradual return to sports should be individualized and instituted by a physician. A daily evaluation by the clinician is recommended at least in the beginning, followed by periodic physician assessments until it is certain that recovery from EHI has occurred. Although strong evidence is lacking, an overabundance of caution is reasonable, especially given the potential for fatality, as illustrated in the abovementioned case reports. It may be prudent to treat an MH patient who has recovered from their event similarly to EHI patients, given the lasting thermoregulatory and metabolic changes that can occur after an acute event. Again, treating recent EHI with extra care during anesthesia is reasonable. To treat them properly, certified athletic trainers and other allied healthcare providers must be able to differentiate exertion-associated muscle cramps, heat syncope, heat exhaustion, exertional heat injury, and EHS. Again, this position statement reinforces the goal of our investigation, to evaluate knowledge in certified athletic trainers and other allied healthcare providers and to initiate education about MH and its role in heat illness in the field.[22]

Awake MH episodes are likely to become more common, given their association with outdoor sports, which are increasing in popularity, climate change, more frequent heat waves, and influenza pandemics. The effect of the coronavirus disease 2019 (COVID-19) on heat illness and awake MH remains to be seen. Recommendations for MH-susceptible individuals include vaccination against influenza and awareness of symptoms of exertional myalgias secondary to physical activities in hot and humid weather, avoiding strenuous or prolonged exercise, particularly in hot environments, and wearing a medical alert bracelet and alerting medical personnel of MH history. Also, due to inevitable delays in the administration of dantrolene, oral doses may be offered to MH or MHS patients so that they can be administered at the earliest possible time to avert a crisis.[23]

Awareness of heat-related illnesses, especially their relationship to MH or MHS, is poor among first responders and community members and non-OR hospital staff. Improving general knowledge about these conditions and treatments will help improve the time to care for these individuals. Consequently, more information and investigations to base further research are needed.

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Conflicts of interest
There are no conflicts of interest.

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Appendix

Survey Questions:

1. What is your occupation?
2. What is your age?
3. What is your gender?
4. In what State or U.S. territory do you practice?
5. How would you describe the area that you coach or care for people?
6. Have you ever seen or treated someone with exercise-induced heat illness?
7. If an athlete complains of body-wide muscle stiffness and pain which of the following would be your first action?
8. If an athlete who had previously complained of generalized muscle stiffness later collapses on the athletic field, what would you do first?
9. An athlete on the field has a family history of difficulty with anesthesia care within the hospital. Could this history link to heat illness on the athletic field?
10. An athlete on the field has a family history of a muscle disease. Does this history link to heat illness on the athletic field?
11. The following diseases or physical situations can be related to heat illness during exercise. List them by number from the most common as number one to the least common as number six.
12. Have you ever heard of malignant hyperthermia?
13. What is malignant hyperthermia?
14. What is dantrolene?
15. An athlete comes to you after practice complaining of cola-colored urine. What is your first action?
16. Can exercise-induced heat illness lead to kidney failure?