The Association of Malignant Hyperthermia and Unusual Disease: When You're Hot You're Hot or Maybe Not

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This issue of *Anesthesia & Analgesia* brings together a collection of papers focused on the prevalence of malignant hyperthermia (MH), the possible association of exertional heat illness with MH, and the association of myotonias, muscular dystrophies, core myopathies, and enzymopathies with MH.[1–7] Although these papers have a global perspective, a number of them originate from a 1-day symposium held during the 2008 Society for Pediatric Anesthesia Spring meeting in San Diego.[1,3–5] The purpose of this symposium was to discuss the relationship of these disorders to MH in light of what is currently understood with regard to their molecular basis and to identify the clinical challenges that these disorders present to pediatric anesthesiologists.

Because a number of case reports and small series have described patients with these disorders and clinical symptoms of increased temperature, arrhythmias, rhabdomyolysis, and/or hyperkalemia during or after anesthesia, the clinician is confronted with the question of whether there is a true association between these disorders and MH. In view of the relative rarity of these disorders, establishing an association between these disorders and MH becomes difficult.

One of the many challenges of providing anesthesia for pediatric patients is that rare or unusual diseases often remain undiagnosed in infancy and early childhood because they have not produced sufficient physiological impairment or clinical signs and symptoms to merit evaluation. This is especially true in pediatric patients with underlying neuromuscular disorders or enzymopathies undergoing anesthesia for muscle biopsies. In addition, critical incidents during anesthesia occur more frequently in infants and small children compared with older children and adults. Airway and cardiovascular instability frequently occurs on induction of anesthesia in infants and small children. Induction of anesthesia by inhalation of potent anesthetic is a method that can facilitate airway management. To further complicate the anesthetic management, IV access is often a challenge in pediatric patients. The need for venous access can become a major determinant of anesthetic technique.

Usually the pediatric patient who presents for a muscle biopsy has only a tentative diagnosis and therefore the risk of MH in this patient is unknown. Part of the dilemma in assessing MH risk in these patients is understanding the limitations in the MH literature and numerous case reports describing adverse anesthetic events. The "gold standard" for confirming a diagnosis of MH has been the *in vitro* contracture test. The sensitivity and specificity of the caffeine halothane contracture test has been determined in patients who did not have clinical myopathy. The sensitivity of a diagnostic test is the probability of that test being positive when the patient has the disease. Specificity of the test is the probability of a negative or normal test result when the patient does not have the disease. Any diagnostic test with high sensitivity has a low false negative rate, and tests with a low specificity have a high incidence of false positives. The

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Table 1. Descriptive Risk of Malignant Upper Trauma[a]

Disease	Risk of MH
Duchenne muscular dystrophy	No increased risk over general population. Weak evidence for MH
Becker dystrophy	No increased risk over general population. Weak evidence for MH
Noonan syndrome	Weak evidence for MH. But closer to zero than dystrophinopathies
Osteogenesis imperfecta	Weak evidence for MH. But closer to zero than dystrophinopathies
Arthrogryposis	Weak evidence for MH. But closer to zero than dystrophinopathies
King Denborough	MHS
Carnitine palmitoyltransferase II deficiency	MHS plausible but unproven. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies. Weak evidence
Myophosphorylase B deficiency (McArdle syndrome)	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myoadenylate deaminase deficiency	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Brody disease	Weak not zero but Rx patients for MH because intracellular Ca^{+2} abnormal. Less risk of MH than in dystrophinopathies
Asymptomatic hyperCKemia	Weak evidence for MH. Increased risk of rhabdomyolysis but less risk of MH than in dystrophinopathies
Myotonia congenita	No increased risk over general population
Paramyotonia congenita	No increased risk over general population
Potassium aggravated myotonia	No increased risk over general population
Myotonia fluctuans	No increased risk over general population
Myotonia permanens	No increased risk over general population
Acetazolamide-responsive myotonia	No increased risk over general population
Hyperkalemic periodic paralysis ± myotonia	No increased risk over general population
Myotonic dystrophy Type I (Steinert disease)	No increased risk over general population
Myotonic dystrophy Type II	No increased risk over general population
Hypokalemic periodic paralysis	Unclear, may be greater risk than in general population but less risk of MH than in dystrophinopathies
Central core myopathy	MHS
Multi-minicore disease with RYR1 mutation	MHS
Multi-minicore disease without RYR1 mutation	MHS less risk of MH than in dystrophinopathies
Nemaline rod myopathy without RYR1 mutation	No increased risk over general population
Nemaline rod myopathy with RYR1 mutation	MHS risk of MH not yet determined

MH = malignant hyperthermia; MHS = malignant hyperthermia susceptibility.

[a] Described in Refs. 1, 3, 4, 5, and 7.

specificity of the caffeine halothane contracture test is about 80%.[8,9] Therefore some patients without MH will have positive contracture tests. Furthermore, the sensitivity and specificity of the caffeine halothane contracture test were determined in patients who did not have other neuromuscular diseases. There is no validation of positive or negative caffeine halothane contracture test cutoff values for MH in patients known to have muscular diseases.

In patients with neuromuscular disease, Adnet et al.[12] reported 28 patients with various neuromuscular diseases and no history of MH or family members with MH who underwent contracture testing. In these patients, they noted a large number of fibers that were depolarized, produced less force when stimulated, and had reduced reactivity when exposed to large concentrations of caffeine. Such muscle does not meet the criteria required for interpretation of the caffeine halothane contracture test. The validity of a caffeine halothane contracture test in patients who have neuromuscular disorders and enzymopathies has been debated because the muscles in these patients may be prone to a positive test on exposure to triggering agents.[10–12]

An alternate to the caffeine halothane contracture test for confirmation of a MH susceptibility (MHS) diagnosis is genetic testing. Unfortunately, genetic testing for MH also has limitations. Genetic testing of MHS has been based on positive caffeine halothane contracture test results. Patients with stronger contracture results than the clinical cutoff for diagnosis of MHS underwent characterization of the ryanodine receptor gene (*RYR1*), most often in a tiered approach, meaning that the exons in which variants are most commonly found were studied first. Only a small number of patients have undergone complete examination of the entire *RYR1* gene. Standard genetic criteria must be met before a variant is identified as causative of MH (see www.emhg.org). At present, more than 300 RYR1 mutations have been documented, and of these, 29 have been formally accepted as causative mutations. Most of the identified variants have not been shown to be causative of MH, because the process of demonstrating *in vitro* that a *RYR1* variant can cause MH requires a significant commitment of resources. Some *RYR1* variants do not alter function of the RYR1 calcium channel, and so they do not cause MH. In addition to *RYR1*, there are two, and

possibly more, genetic loci that have been associated with MHS.[13,14] Presently there is no clinical genetic test that examines these loci. Thus, failure to identify an MH causative mutation in a genetic screening does not rule out the possibility that a patient could be susceptible to MH.

Anesthetic management of pediatric patients presenting for muscle biopsy presents numerous challenges. In addition to the general risks associated with airway management and cardiovascular instability observed in pediatric anesthesia, some pediatric patients with neuromuscular disease have also been reported to have hyperkalemia, cardiac arrests, rhabdomyolysis, and central nervous system alterations after general anesthesia. Occasionally, these patients are labeled as MH or MHS because of these episodes. But hyperkalemic cardiac arrest is not synonymous with MHS. The number of such cases is so few that a valid assessment of the risk of this event and its possible association with MH is not feasible.

Does the choice of anesthetic alter the risks? How does one balance the challenges of venous access difficulty, the risk of losing airway patency, and cardiovascular instability with the possibility that the underlying disorder could increase susceptibility to MH (Table 1)? Because avoidance of triggering anesthetics (inhaled anesthetics and the depolarizing muscle relaxant succinylcholine) is accepted as standard practice for patients with MH or MHS, the use of regional anesthetics and IV drugs has become the preferred anesthetic management for these patients. However, the *sin qua non* of IV anesthesia is the presence of a functioning IV catheter. All too often the patients most in need of the IV catheter are those infants whose venous access is difficult. Should infants whose risk of MH is "weak association" be stressed as they undergo multiple percutaneous IV placement attempts? Should these infants undergo awake cutdowns or intraosseous infusions to achieve venous access? It is not surprising that in the review process of these symposium papers significant differences emerged between the expert reviewers as to the choice of anesthetics and anesthetic approaches for patients whose risk was a "weak association." Some experts maintained that even though some patients do not experience adverse events from exposure to potent inhaled anesthetics, other patients did, and therefore the anesthesiologist should avoid these drugs in all such patients. Other experts maintained that when venous access is a challenge and the risk of MH is weak, brief exposure to inhaled anesthetics during venous cannulation and securing the airway is acceptable practice. If the experts cannot agree, how should less experienced anesthesiologists manage these conundrums?

One potential solution is to quantify risk. One issue in all of these papers is that each set of authors uses different phrases to describe risk. Descriptions of "weak association," and "increased more than the general population" only serve to create a wider gray zone. In the case of children with myopathies undergoing anesthesia, they rarely have hyperkalemia, but often do have increased preoperative creatine kinase levels and rhabdomyolysis may worsen postoperatively. Increased creatine phosphokinase, increased potassium, and myoglobinuria are signs associated with MH but do not define MH. Some of these patients will even have positive contracture tests. If they do not have findings of an increased oxygen consumption or a hypermetabolic state, do these patients have more, less, or the same risk level for MH as the patients with disorders labeled "weak association."

The paper by Benca and Hogan[5] gives a thoughtful approach to these disorders where evidence for an association with MH is weak. However, efforts are still needed to better define risk with more complete clinical data, careful analysis of clinical data from children with myopathies and enzymopathies, and further consensus development to define appropriate anesthetic management for these children.

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