Malignant Hyperthermia-Associated Diseases: State of the Art Uncertainty

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In one form or another, the following scenario is occurring daily in hospitals throughout the world: a 10-mo-old infant with progressive hypotonia and failure to thrive is scheduled for a surgical muscle biopsy and gastrostomy with general anesthesia. The neurological evaluation reveals a differential diagnosis that may include central white matter disease, metabolic encephalopathy, mitochondrial myopathy, or others. The neurologist recommends a nontriggering general anesthetic in the event that the infant is susceptible to malignant hyperthermia (MH). The anesthesiologist performs an uneventful general anesthetic with total IV anesthesia. Regardless of the results of the muscle biopsy, for each subsequent required anesthetic, a nontriggering technique is performed. What is the likelihood that any of these infants is truly MH-susceptible? This month's issue of *Anesthesia & Analgesia* presents a series of articles that helps us answer this question more definitively, though inconclusively, than ever before.

As hotline consultants for the Malignant Hyperthermia Association of the United States (MHAUS),* we commonly receive requests to help clinicians by defining the specific disease entities that predispose to MH susceptibility. With the exception of a small number of inherited conditions, the answer is elusive. With all of our knowledge to date on MH, why is this so? Because in clinical medicine, it is extremely difficult to establish definitive causal relationships without prospective randomized controlled trials, and cohort studies are impossible to perform for rare events. Therefore, we are left with a broad generalization derived from case control studies and case reports and series. To complicate matters, these historical reports did not have the benefit of genetic linkage and pedigree analysis which have, in the current era, furthered the definitive diagnosis of various syndromes and their link to MH.

The path to this specialized issue on MH-associated diseases began several years ago when we and several other MHAUS hotline consultants hosted a series of panel discussions on MH at the annual meetings of the American Society of Anesthesiologists and the Society for Ambulatory Anesthesia. At the 2006 winter meeting of the Society for Pediatric Anesthesia (SPA), Barbara Brandom, Richard Kaplan, and Ron Litman participated on a panel of challenging pediatric MH cases. The response from the audience was overwhelming and clear: "Tell us who should and who shouldn't receive a nontriggering technique." Thus began a 3-yr process that now culminates with the articles presented herein. First, we identified international authoritative experts on each of the broad categories of diseases that have purportedly been linked to MH. Next, we created a partnership between SPA and MHAUS with the purpose of presenting a one-day symposium on MH-related diseases at the 2008 SPA winter meeting.† The organization and implementation of this symposium would not have been possible without the philosophical and financial support of SPA and MHAUS.

By all accounts, the symposium was a resounding success. Each of our authorities presented a lecture on a specific category of disease and the

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*Available at: http://www.mhaus.org.

†Available at: http://www.pedsanesthesia.org/meetings/2008winter/spa08_program.pdf.

evidence with which these diseases are or are not associated with MH susceptibility. Each of the lectures was followed by a lengthy period of audience questions and comments for the experts and between one another. Before the meeting, when we carefully chose the experts and planned the symposium, we hoped to be able to answer the question posed to us by attendees of the previous SPA MH panel and state: "These are the diseases that are associated with MH susceptibility for which you should perform a nontriggering technique." After several presentations, it became apparent that we could not answer this question. In fact, except for a small number of rare inherited diseases, the authorities delivering the lectures were noncommittal, and the experts in the audience could not agree on definitive recommendations. It seemed futile to make definitive recommendations for anesthetic management, and it seemed as if our hopes were dashed. However, following the symposium, something quite unexpected occurred: a large number of practitioners expressed their gratitude to us, not only for giving them concrete recommendations on who should or should not receive a nontriggering technique but also for demonstrating that even the most authoritative MH experts were not sure and could not agree!

Despite this, however, we do know that the phenotype of almost all persons with a genetic susceptibility to MH does not include hypotonia or muscle weakness. Conversely, we also know that there are a limited number of relatively rare disease entities that are closely linked to MH susceptibility. These include central core and multiminicore myopathies, King-Denborough syndrome, and Brody myopathy. Not all patients with these disorders will develop the clinical syndrome, but there is strong clinical and (for central core and multiminicore disease) genetic evidence that the syndromes are linked. For everything else, the evidence is insufficient. Although the true incidence is unknown, boys with Duchenne and Becker muscular dystrophy are at risk for life-threatening hyperkalemia and rhabdomyolysis when anesthetized with MH-triggering drugs. The same cannot be said for the mitochondrial myopathies. Based on clinical reports and the relatively frequent prevalence of this disorder, there is no apparent relation with MH. Other disorders that show no apparent connection to MH include the glycogen storage myopathies and Noonan syndrome. Regarding the myotonias, the pathophysiologic characteristics are varied but have as their basis abnormalities in abnormal structure and function of chloride or sodium channels. Patients with myotonia will likely develop muscle rigidity with succinylcholine that is not related to MH. Patients with myotonic dystrophy do not demonstrate susceptibility to MH, but lack of association is less clear with hypokalemic periodic paralysis.

The most important clue to assessing the risk of MH is a careful history focused on the child's muscular development and performance in relation to his or her peers and a family history of myopathies. Anesthesiologists should be familiar with the clinical course and nature of the more common myopathies and have a ready reference source (e.g., Genetests.org, Orpha.net). It is always more difficult to rule out a negative than to rule in a positive. This holds for the relation between MH and a variety of rarely occurring myopathies with unpredictable clinical courses. Ultimately, with advances in understanding the molecular genetics of a wide variety of disorders, connections will be made between apparently disparate disorders. For example, a recent study has suggested that the pathophysiology of Duchenne muscular dystrophy implicates abnormalities of ryanodine receptor function.[1]

With our current state of knowledge, it is difficult to argue against avoiding potent inhaled anesthetics in any infant with an uncharacterized myopathy. However, by doing this, we engender unnecessary anxiety in the families with regard to their risk of MH. Because MH is inherited as an autosomal dominant disease, labeling one person leads to the labeling of many others. We urge those centers that have a large experience with anesthesia for infants with myopathies to carefully document their experiences and report them in the literature. MH is a complex disorder with many manifestations and many clinically relevant questions that remain unanswered.

REFERENCE

1. Bellinger AM, Reiken S, Carlson C, Mongillo M, Liu X, Rothman L, Matecki S, Lacampagne A, Marks AR. Hypernitrosylated ryanodine receptor calcium release channels are leaky in dystrophic muscle. Nat Med 2009;15:325–30

