A Primer for Diagnosing and Managing Malignant Hyperthermia Susceptibility

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IN this issue, ANESTHESIOLOGY publishes two comprehensive articles on malignant hyperthermia (MH) susceptibility.[1,2] Both highlight the relationship between an anesthetic-induced MH event due to dysregulated skeletal muscle Ca^{2+} homeostasis and an individual's susceptibility to that event. Scientists currently believe that MH susceptibility arises from underlying abnormalities in the *RYR1* (ryanodine receptor 1 on chromosome 19), the *CACNA1S* (calcium voltage-gated channel subunit α1 subunit S receptor on chromosome 1), and/or the *STAC3* (SH3 and cysteine rich domain 3 protein on chromosome 12) genes.

How are abnormalities in three different chromosomes linked to MH susceptibility? Current research suggests that the *RYR1* variants associated with MH susceptibility are missense changes that alter the ryanodine receptor with gain-of-function mutations. These mutations increase calcium release from the skeletal muscle sarcoplasmic reticulum into the cytoplasm. *CACNA1S* variants suppress the calcium voltage-gated channel's regulatory effect on RYR1, similarly causing increased calcium flux through the receptor. STAC3 "chaperone" proteins are required to correctly locate the calcium voltage-gated receptor within the skeletal muscle channel.[3] Mutated STAC3 receptors increase the amount of calcium released in response to caffeine (an RYR1 agonist) and increase the amount of calcium stored within the sarcoplasmic reticulum.[4] Figure 1 in Litman *et al.*[1] depicts the interaction among these receptors and proteins in the skeletal muscle excitation-contraction coupling complex.

Litman *et al.*[1] provide a succinct, clinically relevant discussion of which patients should be considered MH–susceptible due to their underlying diseases.[1] They emphasize that although most MH–susceptible patients appear phenotypically normal, certain phenotypes related to *RYR1* variants may predispose patients to MH, including "central core disease, multiminicore myopathy, congenital myopathy with cores and rods, congenital fiber type disproportion, centronuclear myopathy, and, rarely, King–Denborough syndrome." The authors also note that MH susceptibility associates with STAC3 myopathy (also known as Native American myopathy). The authors address anesthetic management of hypotonic infants and children and suggest genetic evaluation for congenital myopathies and muscular dystrophies before muscle biopsy. If this suggestion were to be implemented, it would decrease the number of hypotonic infants and children managed as MH susceptible, because the majority will be found to have a non-RYR1 etiology.

"...how should we approach the practical dilemma of anesthetizing patients who may be MH [malignant hyperthermia]–susceptible?"

Riazi *et al.*[2] author a narrative review that presents a clear and comprehensive examination of new genetic technologies and approaches for MH diagnosis. The authors analyze and summarize the genetic reasons for MH susceptibility and critically examine the possible connections between RYR1 disorders and anesthetic-induced malignant hyperthermia. The authors emphasize that "genetic and functional characterization are used in combination to assess the pathogenic effect of novel variants" in the *RYR1* and *CACNA1S* genes. However, up to 50% of MH–susceptible individuals do not carry currently known pathogenic variants in the *RYR1* or *CACNA1S* genes. This underscores the continued need to fully characterize MH susceptibility with the specialized MH muscle biopsy test (caffeine halothane contracture test within North America or the *in vitro* contracture test outside of North America).

For those cases in which a proband's MH–causative mutation is not found in a family member, the two articles differ in their guidance. Litman *et al.*[1] state that "family members of . . . probands that do not harbor the same pathogenic variant are not considered MH susceptible." Riazi *et al.*[2] disagree, stating that "MH susceptibility cannot be ruled out for individuals who do not carry the familial variant because of the possibility of more than one pathogenic variant being present in the same family and they

Image: C. Brodoway, Nemours/A. I. duPont Hospital for Children.

Corresponding articles on pages 159 and 168.

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should be offered contracture testing to confirm their MH negative status." The European Malignant Hyperthermia Group's extensive experience with genotyping MH–susceptible individuals and their family members who have *already* been phenotyped by the *in vitro* contracture test supports this stance.[5] In contrast, North American MH researchers' efforts to correctly genotype and phenotype MH families have been handicapped by closure of all but 5 of the MH biopsy centers, which formerly numbered 16.

Of note, the guidance of Riazi *et al.*[2] is more conservative. Some MH–susceptible families carry more than one potentially pathogenic MH variant.[6–8] Further, there is a 5 to 10% discordance between the results of MH genetic mutation analysis and MH diagnostic muscle biopsy.[9] Finally, administering MH–triggering anesthetic agents may produce a fatal outcome. Therefore, I suggest that family members who do not carry the familial genetic mutation either undergo a MH diagnostic muscle biopsy or be managed as MH susceptible. Whenever possible, I believe that the MH diagnostic muscle biopsy should be used to identify those family members whose risk for MH susceptibility is no greater than the risk of the general population. Correct diagnosis reduces patient anxiety and preserves healthcare resources for our other complex patients.

Incorporating the information presented in the articles by Litman *et al.*[1] and Riazi *et al.*,[2] how should we approach the practical dilemma of anesthetizing patients who may be MH–susceptible? Let us proceed to the clinical primer.

Who Should Be Managed as MH–susceptible?

Table 3 in the article by Litman *et al.*[1] serves as a good guide with the modification noted above. Be aware that many MH–susceptible individuals do not have unusual medical conditions but may have an overlooked family history of suspicious anesthetic events. Six percent (16 of 248) to 9.5% (8 of 84) of patients experiencing a "very likely" or "almost certain" MH event had positive MH family histories that were discovered after their MH events. Unfortunately, three patients died during these MH events. For example, after one MH fatality, the family reported that the patient's paternal grandfather had two cardiac arrests during separate general anesthetics.[10,11] Let us collaborate with our surgical and proceduralist colleagues to encourage patients to ask all family members about past adverse anesthetic events before patients meet us for their anesthetics. When we meet our patients, let us also ask the relatives about significant and unexpected familial problems with anesthesia.*

*Support for healthcare professionals is available through the Malignant Hyperthermia Association of the United States (MHAUS) website, www.mhaus.org (click on contact and then healthcare professionals). Contact information for MH biopsy center directors in the United States and Canada may be found at www.mhaus.org. Contact information for MH centers elsewhere may be found at www.emhg.org.

While we should all continue to ask patients preoperatively about their personal experience of significant anesthetic complications, we should remember that prior experience of an unremarkable general anesthetic does not rule out the possibility of MH susceptibility. In a North American MH Registry of the Malignant Hyperthermia Association of the United States (MHAUS) study, the median number of unremarkable general anesthetics before 152 MH events was 2 with a range of 0 to 30.[10]

What Should Be Used for Anesthesia in the MH–susceptible?

Consider anxiolysis before transfer to the operating suite if the patient has a history of any "awake" MH symptoms such as stress or exercise-induced fevers, muscle cramps, or dark-colored urine. This may lessen the likelihood of a perioperative MH event. Use local, regional, or conduction anesthesia when appropriate for the procedure and acceptable to the patient.

If a general anesthetic is desired by the patient or required for the procedure, then no volatile inhalational anesthetics or succinylcholine can be used. Either avoid the anesthesia workstation entirely or use a "clean" anesthesia workstation with activated charcoal filters inserted into the inspiratory and expiratory circuits.[12] Have a plan for managing an obstructed airway that does not include succinylcholine.

For general anesthetics lasting longer than 30 min, use continuous electronic core (esophagus, nasopharynx, tympanic membrane, bladder, or pulmonary artery) temperature monitoring. Hyperthermia is *not* a *late* sign of malignant hyperthermia,[10] and failure to monitor temperature during an MH event increases the relative risk of death 13.8 times.[11]

When Should MH–susceptible Patients Be Anesthetized for Elective Cases?

For elective cases, consider first-case scheduling. Take care of these patients when you are most awake with the greatest number of personnel available. This allows adequate preparation time and decreases the opportunity for critical information to be lost during anesthesia care team transfers or operating room schedule shuffles. The North American MH Registry of MHAUS has received reports of MH events being triggered in known MH–susceptible individuals due to inadequate communication between anesthesia care teams. In addition, first-case scheduling permits extended time for postanesthetic observation should problems arise.

Where Should MH–susceptible Patients Be Managed?

MH–susceptible patients may be anesthetized as outpatients at a free-standing facility if the facility has: (1) intravenous dantrolene availability within 10 min of a decision to use it; (2) the ability to rapidly analyze blood gas and potassium levels to permit treatment of life threatening acidosis and

hyperkalemia; (3) personnel and space to observe patients postoperatively for longer than 1 h if necessary; and (4) a transfer plan to a receiving hospital care facility. MH patients must be stabilized before they are transported to a higher-level facility.[13]

Why Does This Matter?

Malignant hyperthermia events are associated with significant morbidity rates that range from 20 to 35%.[10,14] For each 10-min delay in administration of dantrolene, complications increase substantially. If dantrolene administration is delayed beyond 50 min, complication rates increase to 100%.[14] MH–related complications include neurologic, cardiac, renal, and hepatic dysfunction, pulmonary edema, disseminated intravascular coagulation, and compartment syndrome.[10] More disturbing, U.S. patients continue to die from MH events. A recent North American MH Registry of MHAUS study reports mortality rates as high as 9.5%.[11]

We should all work to avoid preventable MH events in those at high risk for MH susceptibility by adopting the primer's suggestions. In doing so, we will be better prepared to treat the unexpected MH event that we may encounter in the future.†

Competing Interests

The author is a volunteer member of the Professional Advisory Council of the Malignant Hyperthermia Association of the United States. The Malignant Hyperthermia Association of the United States has provided travel expenses to malignant hyperthermia conferences in the United States and Canada.

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†For assistance with MH emergencies, MHAUS MH Hotline Consultants may be reached at 1-800-644-9737 when calling within the United States or Canada or 011-209-417-3722 when calling from countries outside of the United States or Canada.