

Gregory L. Rose, MD;
Thomas McLarney, MD;
Raeford E. Brown, MD
University of Kentucky
College of Medicine,
Lexington

glrose0@uky.edu

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How to avoid this medical emergency

Avoiding an episode of malignant hyperthermia requires that you look for certain clues in a patient's history.

PRACTICE RECOMMENDATIONS

› Suspect malignant hyperthermia (MH) if a patient has night sweats, cramping, mottled skin, low-grade fever, and excessive sweating, or has elevated creatine kinase and rhabdomyolysis on lab studies. **(B)**

› Make sure patients and their family members know that MH is life threatening, familial, and can even occur in patients whose previous experiences with anesthesia have been uneventful. **(A)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

You are asked to perform a preoperative evaluation of a 6-year-old boy who is due to have a tonsillectomy. The family history reveals that his father had an episode that sounds like malignant hyperthermia (MH). Also, a paternal uncle experienced a high fever and almost died after undergoing anesthesia. The boy's parents tell you they took the boy to a pediatrician, who did a "blood test" for MH. They hand you a written report of an enzyme-linked immunosorbent assay, which tested negative for an allergy to succinylcholine.

Has this child been adequately screened for MH?

If you answered No, you are correct. The review that follows explains why.

The "disease of anesthesia"

MH is a pharmacogenetic disease process that occurs when predisposed individuals are exposed to certain triggering agents—specifically, anesthetics. Succinylcholine and all potent inhalational anesthetic agents have been implicated (TABLE 1). Most episodes occur in the intraoperative period.

MH is a familial disease and follows an autosomal dominant pattern, but with incomplete penetrance. Surprisingly, the disease was not described until 1961, when Denborough et al reported a string of anesthetic-related deaths in a family.^{1,2} A similar condition was described in pigs in 1966.³ This condition, porcine stress syndrome, was noted during research in which pigs had received succinylcholine. This syndrome has become the animal model for the study of MH.^{4,5}

Over time, this condition came to be known as malignant hyperthermia because a rapid rise in temperature was a common feature in all reported cases. Additional possible signs and symptoms include skin mottling, arrhythmias, elevated creatine kinase (CK), and rhabdomyolysis, among others (TABLE 2).

■ **Associated conditions.** MH may occur with any condition requiring intervention with anesthesia. It was once believed that strabismus and MH were linked, but this assumption was based

TABLE 1

Triggering and nontriggering anesthetic agents

Triggering agents	Nontriggering agents
Succinylcholine (most common)	Barbiturates
Desflurane	Benzodiazepines
Halothane	Ketamine
Isoflurane	Local anesthetics
Sevoflurane	Nitrous oxide
	Nondepolarizing muscle relaxants
	Opioids
	Propofol

Adapted from: Barash PG, et al, eds. *Clinical Anesthesia*. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2009.

on a statistical error related to an increased number of surgical procedures in children with strabismus. Currently, a propensity toward MH seems associated only with rare myopathic conditions such as central core disease, hypokalemic periodic paralysis, Evans myopathy, and King-Denborough syndrome.⁶ Precise genetic mapping will determine what, if any, relationship there is between these processes and MH.

Awake triggering: Similar disorder without anesthesia

Since 1980 there have been several reports of “awake triggering” in genetically predisposed individuals, whereby stressful conditions alone unrelated to general anesthesia cause MH.⁷⁻¹⁰ Often, the presenting condition has been heat-stroke, but other symptoms are also common, such as rhabdomyolysis, increased CK, muscle pain, and cardiovascular collapse.¹¹ Relatives of those with a history of MH have also exhibited chronic muscle pain or chronic CK elevation. All of these people, when tested, have had a positive reaction to the caffeine-halothane contracture test (CHCT), which is the gold standard for confirming MH.¹²

The Malignant Hyperthermia Association of the United States (MHAUS) lists signs and symptoms that accompany awake triggering on its Web site, www.mhaus.org. They include heat sensitivity, night sweats, cramping, mottled skin, low-grade fever, and excessive sweating.

TABLE 2

Signs and symptoms of malignant hyperthermia

Arrhythmias
Coagulopathy
Elevated creatine kinase
Elevated temperature
Hypercarbia
Hyperkalemia
Increased oxygen consumption
Masseter muscle spasm
Metabolic acidosis
Muscle rigidity
Rhabdomyolysis
Skin mottling
Tachycardia
Tachypnea

Adapted from: Barash PG, et al, eds. *Clinical Anesthesia*. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2009.

Should such findings—especially elevated CK and rhabdomyolysis—come to your attention by a patient’s report or during physical examination, consider further workup for MH.

How MH develops

MH occurs because of a defect in the ryanodine receptor, RYR1. This receptor is responsible for intracellular calcium release by its mediation of the sarcoplasmic reticulum.

CONTINUED



Malignant hyperthermia is a medical emergency and requires that the patient receive dantrolene sodium.

> Malignant hyperthermia can occur as long as 12 hours after exposure to a presumed trigger.

RYR1 is found in all skeletal muscle.¹³ During an episode of MH, exposure to the triggering agent causes intracellular calcium release by the sarcoplasmic reticulum and sustained skeletal muscle contractions and rigidity. Increased oxygen consumption occurs, and this hypermetabolic state leads to hypercarbia, severe metabolic acidosis, tachycardia, arrhythmias, hyperkalemia, and elevated temperature. Rhabdomyolysis and elevations in CK also occur because of skeletal muscle breakdown.

How to treat this medical emergency

Only rapid, specific treatment can save a patient with MH from death. Before investigators discovered that dantrolene sodium is an effective treatment for MH, >70% of patients who developed the disease died.¹² Mortality has since dropped to ≤15%.¹⁴ With a presumptive diagnosis of MH, dantrolene should be prepared and given immediately. The drug inhibits the release of calcium from the sarcoplasmic reticulum of skeletal muscle by limiting the activation of RYR1.

Successful resuscitation of patients with MH hinges on the following:

■ **Making a prompt diagnosis.** While most episodes of MH occur shortly after induction of anesthesia or during the intraoperative course, nearly 2% of MH cases occur postoperatively¹⁵—some as long as 12 hours after exposure to the presumed trigger.

■ **Immediately discontinuing triggering anesthetics and starting dantrolene.** The patient should be kept anesthetized using nontriggering agents (TABLE 1), and surgery should be concluded as quickly as possible.

Preparation of dantrolene is a tedious process because of its poor water solubility. One to 2 minutes are needed for the preparation to solubilize. Initial treatment with dantrolene is 2.5 mg/kg administered intravenously (via peripheral or central line). This dose (or up to 10 mg/kg) can be repeated every 5 to 10 minutes until major symptoms such as hypercarbia, arrhythmias, hyperpyrexia, and metabolic acidosis abate. Thereafter, dantrolene is continued at 2.5 mg/kg every 4 hours for 24 hours.

■ **Cooling the patient.** A patient should be cooled using ice packs, gastric lavage with ice

Incidence of MH is increasing

The number of reported cases of malignant hyperthermia (MH) has increased over the last 20 years, but the exact incidence is unknown. It varies not only by country, but, within the United States, from state to state, and even within states, presumably due to variations in the genetic pool. Michigan, Nebraska, West Virginia, and Wisconsin report especially high incidences.¹⁹

MH is more common in men than women (58% vs 42%, respectively, of affected patients). The last major survey of MH incidence was published in 2009.²⁰ In the survey years (2000-2005), MH incidence increased from 10.2 to 13.3 patients per million hospital discharges. Mortality in the same period decreased from 16.1% to 6.5%.

water, cold intravenous fluid, or ice water lavage at the surgical site. Active cooling should stop when the patient's temperature reaches 100°F (so as not to cause hypothermia). Cooling should not, however, prevent or slow the administration of dantrolene.

■ **Treating acidosis, arrhythmias, electrolyte disturbances, coagulopathy, excess myoglobin, and acute renal failure.** Arrhythmias should not be treated with calcium channel blockers.

■ **Monitoring patients in the ICU** for potential adverse effects of dantrolene that can include sedation and muscle weakness. Mechanical ventilation may be needed. (The malignant hyperthermia hotline [800-644-9737] at MHAUS is available 24 hours a day to assist clinicians with questions regarding diagnosis and treatment.)

Keeping patients safe by properly testing them

The CHCT is 97% sensitive and 78% specific for MH.¹⁶ It is an invasive procedure, requiring the patient to undergo anesthesia. The test costs more than \$5,000, which most insurance companies will cover.¹⁷

The CHCT is performed only on fresh muscle, and only 5 centers in North America perform the test. The number of centers is kept to a minimum to maintain high procedural quality. The biopsy specimen is taken from the

vastus lateralis. Because of the size of the specimens required to perform the test, a child weighing <20 kg or <5 years of age is usually not tested but simply presumed to be MH susceptible.¹⁸

Counseling patients and their families

Make sure affected individuals and family members know the life-threatening implications of this condition; that it is familial and that its onset does not always occur with a first exposure to anesthesia, but sometimes with a subsequent exposure. Explain that MH is not an "allergy to anesthesia" or an "allergy to succinylcholine." Patients can undergo anesthesia safely in the future if performed with a nontriggering agent and associated technique. Anesthesiologists today are well trained to manage these patients with minimum risk.

Counsel first-degree relatives of MH patients about undergoing the CHCT. Molecular genetic testing, which requires a blood draw but is less sensitive than the CHCT, may be another option. If an MH patient was diagnosed using this blood test, relatives may opt to be tested this way, as well. If genetic test results for relatives are positive, these individuals are presumed to have MH and should be treated as such, saving them the expense and risk of undergoing muscle biopsy. If genetic test results are negative, the CHCT should be considered or patients

should be presumed to be MH susceptible.

Why is testing of relatives needed if a nontriggering anesthetic can be administered? Nontriggering anesthetic agents are not routinely used in surgery, and problems can arise in, say, emergency situations when MH susceptibility in a patient is unknown to the surgical team. Testing enables patients to learn their status and to obtain a medical alert bracelet.

What about the child in the opening scenario?

It is evident that the child in the scenario at the beginning of this article was not adequately screened for MH. Given that the child is >5 years of age, he should undergo the CHCT. You would be wise to presume that his first-degree relatives are also susceptible until proven otherwise by the CHCT. With children not meeting the age or weight requirement for CHCT, make sure the family understands the potential severity of MH and immediately inform the surgeon and anesthesiologist of the family history so appropriate precautions, including arrangements for nontriggering anesthetics, can be put into place. **JFP**

CORRESPONDENCE

Gregory L. Rose, MD, Department of Anesthesia, University of Kentucky College of Medicine, 800 Rose Street, Lexington, KY 40536; glrose0@uky.edu

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