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Malignant Hyperthermia
A Clinical Review

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Keywords

• Malignant hyperthermia • Perioperative management • Signs
• Associated disorders • Genetics

Key points

- Malignant hyperthermia (MH) is a pharmacogenetic disease of skeletal muscle that presents as a progressively worsening hypermetabolic response in susceptible individuals exposed to triggering anesthetic agents.
- Genetic mutations in a few key genes lead to disordered calcium homeostasis during a triggering anesthetic, causing muscle rigidity, increased carbon dioxide production, and acidosis that, left untreated, can lead to cell lysis, hyperkalemia, arrhythmias, and death.
- Early recognition and prompt treatment with the antidote drug dantrolene is vital to minimize morbidity and mortality.
- Genetic testing and research have been essential in characterizing the disorder, establishing loci of pathogenic mutations, and elucidating the connection between MH and other diseases, but contracture testing remains the gold standard in establishing a patient's MH status.

INTRODUCTION

Malignant hyperthermia (MH) is an uncommon and potentially life-threatening genetically based disorder of skeletal muscle that occurs in susceptible individuals on exposure to halogenated volatile anesthetics and/or the depolarizing muscle relaxant, succinylcholine. Rarely, an MH episode may be triggered in certain individuals by rigorous exertion or heat stress [1]. Almost all patients who are MH susceptible show no clinical signs or symptoms of MH until they are challenged with triggering agents [2,3]. On

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exposure to triggering agents, disordered calcium homeostasis in skeletal muscle cells leads to a hypermetabolic response shown by muscle rigidity, tachycardia, hypercapnia, and rapidly increasing temperature. As the metabolic needs of the cells outstrip ATP supplies, lactic acidosis ensues, leading to metabolic acidosis and eventual cell lysis and resulting in diffuse rhabdomyolysis, hyperkalemia, disseminated intravascular coagulation (DIC), ventricular arrhythmias, and death [4]. Historically, the morbidity and mortality of MH episodes was high, with mortalities reported to be as high as 70%. Research efforts led to the discovery of the antidote drug, dantrolene, the use of which has reduced the mortality of MH episodes to less than 5% [3,5]. Despite the decrease in risk of death, the morbidity rate was reported in 2010 as 34.8% by Larach and colleagues [6]. Definitive diagnosis has relied on muscle biopsy and contracture testing for the past 30 years. Further genetic research has greatly expanded the knowledge of the disorder and has caused some clinicians to question the utility of continuing contracture testing. Some argue that the ready availability and clinical efficacy of nontriggering intravenous (IV) anesthetic agents could relegate concerns over MH into medical history. The authors argue that inhalational anesthetics remain clinically relevant and indicated for a large number of patients, and contracture testing remains essential despite advances in genetic testing. Furthermore, recent research shows an unanticipated increase in mortality from the disease, which compels us to publish this clinical review [7]. This article discusses pathophysiology, genetics, epidemiology, diagnosis, and treatment of MH in the modern medical setting.

PATHOPHYSIOLOGY

Muscle contraction and relaxation is a complex neurochemical process that is tightly controlled in myocytes. During excitation-contraction coupling, there is a conformational change in the T-tubular voltage-gated calcium channel, called the dihydropyridine receptor (DHPR), induced by muscle membrane depolarization. This change causes activation of the ryanodine receptor type 1 (RYR1), leading to a rapid release of calcium from the sarcoplasmic reticulum, and muscle contraction is initiated. Muscle relaxation occurs when the ATP-dependent pump drives calcium back into the sarcoplasmic reticulum [8,9].

The underlying mechanism of MH is related to an uncontrolled release of calcium from skeletal muscle sarcoplasmic reticulum [10,11]. The sarcolemmal sodium-calcium pump reincorporates calcium via aerobic metabolism, but the sustained release of calcium overwhelms the pump: this is the metabolic engine driving the MH response. The hypermetabolic response leads to increases in oxygen consumption, carbon dioxide production, and heat generation. Once ATP stores are depleted, anaerobic metabolism accelerates acidosis and, if untreated, progresses to the failure of cellular membrane integrity and myocyte death, leading to the leakage of cell contents including potassium, myoglobin, and creatinine kinase [8].

CLINICAL DESCRIPTION

The clinical presentation of MH can vary. It can be difficult to diagnose MH with confidence in the absence of diagnostic testing, especially while the patient is receiving general anesthesia [12]. All halogenated inhalational anesthetic agents currently in use (isoflurane, sevoflurane, desflurane) are potential triggering agents for MH. Succinylcholine, a depolarizing neuromuscular relaxant, is also a known triggering agent. Studies in pigs validate succinylcholine as a trigger, and it is known that succinylcholine can potentiate the MH reaction from volatile anesthetics [13]. No other anesthetic agents, including nitrous oxide, currently in use have been identified as potential triggering agents [2].

MH most often occurs intraoperatively with exposure to triggering agents. It can present in the early postoperative period, but in most cases review of the anesthetic record reveals that diagnostic clues were present sooner. Because MH is a muscle-based hypermetabolic process, the hallmark of MH is increased carbon dioxide production. When a patient's ventilation is being controlled, the clinician has to adjust ventilator parameters to compensate for elimination of this additional carbon dioxide, which should be an early indication of a potential MH crisis. In cases in which a patient is breathing spontaneously, increased minute ventilation may go unnoticed until the production of carbon dioxide exceeds the patient's ability to compensate, contributing to delay in diagnosis [14].

Another early sign of MH is unexplained sinus tachycardia. Because sinus tachycardia is a common and nonspecific sign, it may be misdiagnosed as being caused by a light plane of anesthesia or inadequate pain control. Tachycardia combined with hypercarbia is highly suspicious of a hypermetabolic state, and an evaluation to confirm or exclude MH should be ruled out by assessing the patient for muscle rigidity, acidosis, or hyperkalemia [15].

Hyperthermia is a key indicator of MH, but it can be a late sign or may be absent [16]. However, rapidly increasing core temperature is more commonly noted if hypermetabolism is present for any significant period of time. Delay in diagnosis and hyperthermia greater than 39°C has been shown to increase the risk of morbidity from organ dysfunction/failure and from DIC. Isolated temperature increases at any point, unaccompanied by associated signs of hypermetabolism (hypercarbia/tachycardia), are unlikely to be MH [17]. Skin liquid crystal temperature indicators have failed in numerous reports and their use should be discouraged in favor of more reliable patient temperature monitoring.

Generalized muscle rigidity is seen in 50% to 80% of patients, caused by muscle contraction, and is an important and highly specific sign of MH [1]. Rhabdomyolysis, breakdown of skeletal muscle, is a late sign of MH and can result in life-threatening hyperkalemia. Myoglobinuria from rhabdomyolysis may also lead to acute renal failure [18].

Other clinical signs of MH may include hypoxemia, pulmonary edema, congestive heart failure, cardiac arrhythmias, electrolyte imbalances, and alterations in consciousness [3].

Medical conditions such as sepsis, pheochromocytoma, neuroleptic malignant syndrome, serotonin syndrome, and thyroid storm may resemble the pattern of MH and may be difficult to differentiate on clinical basis alone [8].

Treatment algorithim

If feasible, end surgery as soon as possible, and stop all triggering agents.

If surgery must proceed, begin nontriggering anesthetic with IV agents.

Call for help, and obtain dantrolene and MH supplies. Call emergency services if transfer to tertiary facility is required for intensive care unit (ICU)–level care. Call the Malignant Hyperthermia Association of the United States (MHAUS) Hotline for assistance 24/7 (1-800-644-9737).

Hyperventilate and use high flows of oxygen at fraction of inspired oxygen 1.0 to flush volatile anesthetics from the breathing circuit and to help quickly decrease end-tidal CO2 (ETCO2). Use inline charcoal filters, if available, to quickly scrub trace gases from the circuit.

As soon as possible, administer dantrolene 2.5 mg/kg IV. If using standard dantrolene, mix the drug using 60 mL of sterile water. Several assistants may be necessary. Administer each vial as soon as reconstituted until the loading dose is complete. Additional dantrolene may be given up to 10 mg/kg as needed to decrease ETCO2, stabilize vital signs, or end rigidity. Ryanodex (lyophilized preparation of dantrolene) requires 5 mL of sterile water per 250 mg.

Laboratories should include arterial blood gas (ABG), serum potassium, and creatine kinase (CK) levels, along with urine myoglobin level. Follow ABGs for resolution of acidosis. Repeat CK measurements every 6 hours until returned to normal in order to diagnose and treat possible rhabdomyolysis.

Actively cool the patient if core temperature is increased. Stop cooling when the temperature has decreased to less than 38_C, to avoid hypothermia. Patients can be cooled with ambient air; ice packs to groin, axilla, and head; intraperitoneal lavage; or Cardiopulmonary Bypass.

Treat hyperkalemia with calcium, glucose, and insulin, as well as bicarbonate as necessary.

Avoid calcium channel blockers in the treatment of arrhythmias, because they can precipitate hyperkalemia and cardiac collapse.

Give IV fluids/diuretics to ensure greater than 1 mL/kg/h urine output. Dantrolene has small amount of mannitol added as a buffering agent; more may be required if rhabdomyolysis present. Treat acidosis and hyperkalemia if present (discussed earlier).

If CK or Kþ level increases, assume myoglobinuria is present and give bicarbonate infusion of 1 mEq/kg/h, to alkalinize urine.

Continue to monitor urine output, core temperature, ETCO2, and pH as indicated. Arrange for transport to a critical care setting as symptoms resolve.

TREATMENT

The antidote drug, dantrolene, was approved by the US Food and Drug Administration in 1979 for use in MH crisis. It is a muscle relaxant drug

that acts as an antagonist at the ryanodine receptor to slow the release of calcium and to allow the cells to reincorporate it into the sarcoplasmic reticulum. Given as a loading dose of 2.5 mg/kg IV, it rapidly slows the hypermetabolic process involved in MH. There are 2 commonly dispensed preparations. The standard preparation is Dantrium, available in 20-mg vials that require 60 mL of sterile water to reconstitute. Giving a 2.5-mg/kg loading dose to the average 100-kg patient requires multiple providers to proceed efficiently. A newer, more concentrated preparation is Ryanodex, supplied in vials containing 250 mg of dantrolene requiring only 5 mL of sterile water to reconstitute. Some clinicians question the cost-effectiveness of routinely stocking dantrolene, given the low incidence of MH, the cost of the drug (higher with the Ryanodex), and the limited (3-year) shelf life. A recent review [19] confirms dantrolene's cost-effectiveness compared with supportive care alone in the outpatient setting. MHAUS strongly recommends stocking dantrolene at any facility in which triggering agents are being used.

Before dantrolene use became widely popular in the early 1980s, only 36% of patients survived when treatment was limited to the symptoms of MH [20]. Modern MH mortality in patients less than 18 years old ranges from 0.66% to 4.6% [20–23]. A significantly lower mortality is reliably shown in children versus adults, possibly secondary to earlier diagnosis and treatment. According to National Inpatient Sample (NIS) data, mortality for adults (14.1%) was significantly higher than in pediatric patients (0.7%). Mortality did significantly increase as the number of comorbidities increased in the adult and pediatric populations [24]. The significantly better mortality seen in pediatric versus adult patients is directly attributable to early recognition and treatment with dantrolene. Another explanation for the improved mortality is the decreased use of succinylcholine in the pediatric population [24]. Statistically significant higher mortality has been observed among pediatric patients in the southern United States, those with higher comorbidities, in patients transferred between facilities, or those listed as having been admitted through the emergency department [24]. In addition, an alarming complication rate (35%) still exists for MH-treated patients [6]. Studies have shown that complication rates and morbidity increase with a muscular build, with increased time between induction and highest ET_{CO_2}, and with development of DIC. Only 6.5% of patients had a prior family history of MH [20].

An attempt should be to collect blood for laboratory electrolyte and CK analysis before dantrolene is given, to assist in confirming the diagnosis. Clinicians should be cautious with extreme cooling measures in children because the cutaneous vasoconstriction seen with intense cooling may reduce the ability to discharge heat and reduce skeletal blood flow, contributing to worse patient outcomes. Despite decreases in MH-related mortality and improved MH recognition in recent decades, fatal MH cases still occur because of the variable presentation, lack of dantrolene availability or administration, and inappropriate or incomplete treatment [25].

Dantrolene is well tolerated clinically, although side effects do occur in up to 21.6% of treated patients. The most commonly described side effect is muscle weakness, and patients treated with high doses of dantrolene may require ventilator support. Phlebitis, rash, and transaminitis have also been described [22].

RECRUDESCENCE

Recrudescence is the recurrence of MH symptoms following successful initial treatment. In one study, recrudescence occurred in 14.4% of patients less than 18 years old and in 19.1% of children less than 12 years old [22]. A second study found the recrudescence rate to be 20% for all pediatric patients, and slightly higher at 29% for children less than 12 years old [26]. Two cases were fatal: one occurred in a 4-year-old 6 hours after initial MH symptoms resolved, and the second case was in a 14-year-old in whom symptoms recurred 24 hours after initial symptom resolution [22]. The North American MH Registry (NAMHR) database found the mean onset time for recrudescence to be 13 hours in 308 pediatric patients; 73% of these patients were male. Further analysis showed that recrudescence was more likely with a muscular body type, Clinical Grading Scale (CGS) score greater than 35, greater than 150 minutes from induction to peak symptoms, or presence of a temperature increase noted with initial symptoms [27].

It is critical for anesthesiologists to consider recrudescence following initial treatment and to take an active role in managing the ICU courses of patients with MH. The risk of recrudescence increases with greater muscle mass, and can occur at times remote from initial treatment and apparent recovery [26].

EPIDEMIOLOGY

A clear understanding of MH has been challenged by the dominant reliance on case reports and retrospective studies. It is not possible to perform prospective randomized human trials because of the ethical concern of exposing susceptible patients to a known trigger. Understanding MH risk factors, prevalence, and outcomes requires very large databases to account for the rarity of the disease and the variability in its presentation [21].

Multiple databases exist and have been used to analyze data regarding MH, including the NAMHR, which was established in 1987 and merged with the MHAUS in 1995 so that data on MH could be stored in a single site. In addition, the Kids' Inpatient Database (KID) is the largest publicly available all-payer pediatric inpatient care database in the United States, containing information from approximately 3 million pediatric discharges each year. The KID has been produced every 3 years from 1997 to 2016. Pediatric data have also been extracted from the NIS, which is another publicly available all-payer inpatient health care database in the United States that includes pediatric hospital inpatient stays not including outpatient surgery. Extremely large databases such as these have been successfully used to analyze MH data. The International Classification of Disease, Ninth Version (ICD-9), code for MH (995.86) was

introduced in 1998. However, there are inherent risks and missed patients with retrospective database reviews that have been based on ICD-9 coding. Despite MH having a unique ICD-9 code, it is probable that some patients were either misdiagnosed or miscoded.

INCIDENCE/MORTALITY

The exact clinical incidence of MH is unknown, but it is estimated that MH occurs in 1 in 15,000 children and 1 in 50,000 adults undergoing an anesthetic [5]. The incidence reported in the literature varies widely; from 1:14,000 anesthetics put forth by Britt [5] to the values reported by Rosero and colleagues [24] of 1 to 1.3 per 100,000, or by Li and colleagues [23] at 3 per 100,000. The 13 years of data reviewed by Salazar and colleagues [21], using NIS and KID data, revealed an incidence of 0.1 per 100,000, whereas Brady and colleagues [28] analyzed New York State date over a 5-year period and reported an incidence of 1 per 100,000, but found the MH risk significantly higher in men than in women. New York State inpatient data from 2001 to 2005 showed a consistent MH incidence among pediatric patients less than 18 years old. The MH rate was 1 in 100,000 for surgical anesthetics, and 4.4 in 100,000 for nonsurgical anesthetic cases [28].

Prevalence analyzed by age shows that children between the age of 1 and 4 years had an increased prevalence of 5.6 in 100,000 compared with all pediatric patients. Boys were 3 times more likely at 4.9 versus 1.6 in 100,000 for girls ($P<.00001$), but the sex difference for MH prevalence was not seen in infants. In addition, no differences were seen in pediatric MH prevalence with regard to race, year of admission, and admission type; that is, scheduled versus unscheduled [23]. Of note, cases of MH among pediatric patients were approximately equally split between pediatric hospitals and nonpediatric hospitals [21].

The prevalence of genetic variants or mutations that make an individual MH susceptible is estimated to be between 1 in 2000 and 1 in 3000, which is notably discrepant and higher than the incidence of clinical MH [29]. MH is thought to follow an autosomal dominant pattern of inheritance with incomplete penetrance and variable expression [30–33]. Incomplete penetrance of a genetic trait means that the phenotype may not be expressed in every individual that carries the allele, and that it may require additional factors for expression of the disease phenotype. This finding may be caused by multiple genes operating together or against each other to express a certain phenotype. Variable expression means that individuals carrying the same allele may display different phenotypes. There is evidence for the presence of genetic factors influencing penetrance and expression, but specific factors are poorly understood. Incomplete penetrance and variable expression make the disorder even harder to characterize [34,35]. The discrepancy between the clinical incidence of MH and the prevalence of genetic susceptibility variants may be explained by these complex patterns of inheritance and expression [29].

MH may develop when a susceptible individual is exposed to a trigger for the first time; however, susceptible patients on average undergo 3 anesthetics

before the episode occurs [3]. MH has been reported worldwide, affecting all ethnicities [8].

GENETICS

Three genes have been identified as associated with MH susceptibility. The RYR1 gene (chromosome 19q13) was the first gene that was linked to MH susceptibility. Since then, it has been established as the major gene responsible for the disorder [36]. Ryanodine receptors (RYRs) are a family of intracellular calcium release channels, with RYR1 being the isoform that is predominantly found in skeletal muscle. A small number of susceptible families carry a mutation in CACNA1S gene (chromosome 1q32), which encodes for the alpha-1S subunit of DHPR, another gene responsible for MH [37–39]. Most recently, a variant of the STAC3 gene, which encodes a protein important for excitation-contraction coupling via trafficking the voltage sensor into the correct T-tubular location, has been reported to cause a congenital myopathy associated with MH susceptibility in a Native American family [40,41]. More than 200 variants or mutations of RYR1 gene were found to be associated with susceptibility for MH; however, only 35 RYR1 variants and 2 CACNA1S variants are considered to be causal and functionally characterized for genetic testing [3,29]. Only 50% to 70% of cases of MH are associated with either variants of the RYR1 and/or CACNA1S genes, and the rest of the remaining cases do not have an associated known gene variant [32,42,43]. As such, research is ongoing.

Calsequestrin-1 (CASQ1) is a calcium-binding protein located in the sarcoplasmic reticulum terminal cisternae of striated muscle. It had been implicated as a potential gene for MH susceptibility. However, most recent evidence suggests that it is unlikely to be a major MH-susceptible locus in humans [44–46].

The heterogeneity of RYR1 variants identified via genetic testing make sole reliance on genetic testing for establishing MH status problematic. As stated, at least 30% of tested individuals show no mutations in RYR1 or CACNA1S, and the estimated false-negative rates in genetic testing are around 3% [35,47]. As more mutations are identified, contracture testing remains the best method of confirming phenotype in susceptible individuals.

CONTRACTURE TESTING

The authors adhere to the testing algorithm proposed by the European Malignant Hyperthermia Group (Fig. 1). Genetic testing may proceed first, and, if a pathogenic variant is identified, the patient is considered susceptible. Contracture testing should proceed only after a recovery period of 6 to 8 weeks has elapsed in patients who have had a clinical episode. Patients that desire muscle biopsy and testing in North America must present to one of only 5 biopsy centers for the procedure (Table 1 and Box 1). Using regional block or nontriggering general anesthesia, a $3.5 \times 1.5 \times 1.5$ cm sample is excised from the vastus muscle of the thigh. The specimen is dissected into individual muscle bundles that are mounted in a series of Krebs solution baths. The bundles are

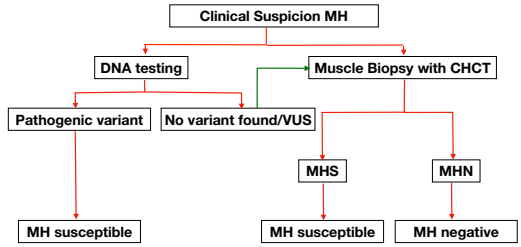

Fig. 1. Treatment algorithm. CHCT, caffeine halothane contracture test; MHN, MH negative; MHS, MH susceptible; VUS, variant of unknown significance. (*From* Girard, T. Diagnostic Pathway. European Malignant Hypertension Group. Available at: https://www.emhg.org/testing-for-mh/2017/12/27/diagnostic-pathway.)

stimulated via electrodes after optimal polarity and optimal lengths are calibrated using measurement of maximal twitch tension. Three baths are exposed to incremental doses of caffeine (0.5, 1, 2, 4, 8, 32 mM) and 3 baths are exposed to 3% halothane. Baseline muscle tension is measured, and any bundle showing increased tension greater than the threshold (0.3-g contracture at 2 mM caffeine, >0.5-g increase during halothane) is defined as MH susceptible. Reported sensitivity and specificity for the North American protocol are 97% and 78%, respectively [48]. Given the protocol's high sensitivity, a negative result has a high negative predictive value.

There are several barriers to testing. The test requires viable muscle, so many patients must travel long distances to biopsy centers that are widely spaced across North America (Box 2). Health insurance coverage is functionally essential for test access, because facility fees at testing centers make the test cost prohibitive otherwise for most. Even so, although insurance pays for testing, travel costs are borne entirely by the patients and families. These barriers contribute to low volumes at most centers, which can then contribute to challenges with the consistency of staff and equipment. The relative ease of use and clinical efficacy of nontriggering anesthetics has made some clinicians raise the question of whether to test patients at all. Given clinical suspicion or family history, patients could simply be treated using nontriggering techniques and avoid the cost and inconvenience of contracture testing. The authors counter with the arguments that patients with unresolved MH status continue to face barriers to care in many communities, given the common requirement of testing before treatment. They may also encounter career limitations and increased insurance costs. In addition, volatile anesthetics and succinylcholine remain ubiquitous and have strong clinical utility in many situations. Contracture testing resolves most of these issues.

PEDIATRICS, ASSOCIATED DISEASES, AND COMORBIDITY

In children scheduled for an anesthetic, too often there exists confusion as to whether they are MH susceptible. Extensive efforts have been made in

Table 1
Clinical indicators for use in determining the malignant hyperthermia raw score

Process	Indicator	Points
Process I: rigidity	Generalized muscular rigidity (in absence of shivering caused by hypothermia, or during or immediately following emergence from inhalation general anesthesia)	15
	Masseter spasm shortly following succinylcholine administration	15
Process II: muscle breakdown	Increased CK level >20,000 IU after anesthetic that included succinylcholine	15
	Increased CK level >10,000 IU after anesthetic without succinylcholine	15
	Cola-colored urine in perioperative period	10
	Myoglobin in urine >60 μg/L	5
	Myoglobin in serum >170 μg/L	5
	Blood/plasma/serum K^b >6 mEq/L (in absence of renal failure)	3
Process III: respiratory acidosis	PET_{CO_2} >55 mm Hg with appropriately controlled ventilation	15
	Arterial Pa_{CO_2} >60 mm Hg with appropriately controlled ventilation	15
	PET_{CO_2} >60 mm Hg with spontaneous ventilation	15
	Arterial Pa_{CO_2} >65 mm Hg with spontaneous ventilation	15
	Inappropriate hypercarbia (in anesthesiologist's judgment)	15
	Inappropriate tachypnea	10
Process IV: temperature increase	Inappropriately rapid increase in temperature (in anesthesiologist's judgment)	15
	Inappropriately increased temperature >38.8°C (101.8°F) in the perioperative period (in anesthesiologist's judgment)	10
Process V: cardiac involvement	Inappropriate sinus tachycardia	3
	Ventricular tachycardia or ventricular fibrillation	3
Process VI: family history (used to determine MH susceptibility only)	Positive MH family history in relative of first degree[a]	15
	Positive MH family history in relative not of first degree[a]	5
Other indicators that are not part of a single process[b]	Arterial base excess more negative than −8 mEq/L	10
	Arterial pH <7.25	10
	Rapid reversal of MH signs of metabolic and/or respiratory acidosis with IV dantrolene	5
	Positive MH family history together with another indicator from the patient's own anesthetic experience other than increased resting serum CK level[a]	10
	Resting increased serum CK level[a] (in patient with a family history of MH)	10

Abbreviation: $PETCO_2$, partial pressure of $ETCO_2$.

[a] These indicators should be used only for determining MH susceptibility.

[b] These should be added without regard to double counting.

From Larach MG, Localio AR, Allen GC, et al. Anesthesiology. 1994 Apr;80(4):771-9. A clinical grading scale to predict malignant hyperthermia susceptibility; with permission.

Box 1: Scoring rules for the malignant hyperthermia clinical grading scale

MH indicators

Review the list of clinical indicators. If any indicator is present, add the points applicable for each indicator while observing the double-counting rule below, which applies to multiple indicators representing a single process.

If no indicator is present, the patient's MH score is zero.

Double counting

If more than 1 indicator represents a single process, count only the indicator with the highest score. Application of this rule prevents double counting when 1 clinical process has more than 1 clinical manifestation.

Exception: the score for any relevant indicators in the final category of Table 1 (other indicators) should be added to the total score without regard to double counting.

MH susceptibility indicators

The italicized indicators listed below apply only to MH susceptibility. Do not use these indicators to score an MH event. To calculate the score for MH susceptibility, add the score of the italicized indicators below to the score for the highest-ranking MH event.

Positive family history of MH in relative of first degree

Positive family history of MH in relative not of first degree

Resting increased serum creatinine kinase level

Positive family history of MH together with another indicator from the patient's own anesthetic experience other than increased serum CK level

Interpreting the raw score: MH rank and qualitative likelihood

Raw score range	MH rank	Description of likelihood
0	1	Almost never
3–9	2	Unlikely
10–19	3	Less than likely
20–34	4	Greater than likely
35–49	5	Very likely
50+	6	Almost certain

From Larach MG, Localio AR, Allen GC, et al. Anesthesiology. 1994 Apr;80(4):771-9. A clinical grading scale to predict malignant hyperthermia susceptibility; with permission.

Box 2: Contracture testing centers in North America

Toronto General Hospital, Toronto, Ontario, Canada

Uniformed Services University of the Health Sciences, Bethesda, MD

UC Davis MH Biopsy Testing Center, Sacramento, CA

University of Minnesota, Minneapolis, MN

Wake Forest Baptist Medical Center, Winston-Salem, NC

mapping the genetic information for a host of myopathic conditions that before now were associated with MH via rare case reports. The overarching theme is that myopathies genuinely associated with MH almost invariably are in individuals with RYR1 gain-of-function mutations, or, more infrequently, CACNA1S. Gain-of-function mutations are those that shift systems toward threshold levels. The disorders most likely directly linked are central core disease (CCD) and King-Denborough syndrome. CCD is often diagnosed in early infancy with generalized weakness and skeletal deformities. Affected infants show dominantly inherited RYR1 variants with MH phenotype. Second, King-Denborough syndrome is extremely rare and is associated with dysmorphic features and skeletal anomalies, including kyphoscoliosis, pectus carinatum, and short stature, and myopathy [25,49–51]. They too show RYR1 mutations with MH phenotype [52].

The most commonly reported associated diagnosis in pediatric MH cases is rhabdomyolysis, which occurred in 26% of the cases in the KID and NIS datasets. Muscular dystrophy and mitochondrial disorders were the most common comorbidity, but most often do not truly represent MH. Dystrophic muscle (Duchenne and Becker muscular dystrophy) can show rhabdomyolysis and brief rigidity on exposure to inhalational anesthetics and catastrophic hyperkalemia from rhabdomyolysis following succinylcholine administration, but that is not MH [52].

Hypotonia is a common diagnosis in children and presents a unique challenge to anesthesiologists. Most hypotonia in children is either central in origin (central nervous system dysfunction secondary to chronic hypoxic ischemic encephalopathy) or secondary to chromosomal abnormalities such as trisomy 21. Hypotonia in pediatric patients does not increase MH susceptibility, and a nontriggering anesthetic is not necessary [52]. Younger patients were more likely to show muscle weakness, undescended testes, and inguinal hernia [22].

Case reports of confirmed MH episodes in the absence of triggering agents have led some investigators to search for a link between MH, exertional rhabdomyolysis (ER), and exertional heat illness (EHI) [53,54]. The conditions share many clinical similarities, including increased core temperatures, muscle rigidity, tachycardia, tachypnea, increased CK level, hyperkalemia, myoglobinuria, acute renal failure, and DIC. Dantrolene has proved an effective treatment in cases of EHI. Interestingly, cohort studies have shown MH-associated RYR1 mutations in up to 30% of patients with ER studied [54]. However, when MH pedigree families are queried, even those with mutations known to be highly pathogenic, no increased rates of ER or EHI are found. Further, when patients with a history of either ER or EHI are studied, most mutations found are variants of unknown significance [30]. Patients with history of ER/EHI and RYR1 mutations may simply have overlapping but causally unlinked diagnoses. Further investigation is warranted, and patients with ER/EHI should have detailed genetic analysis looking for RYR1 and CACNA1S mutations, along with screening for myopathy/rhabdomyolysis disorders.

Children often show a heterogeneous presentation of MH, and their diagnosis can be delayed [55]. In 1994, Larach and colleagues [56] developed a CGS for MH recognition using clinical indicators to predict the likelihood of an MH event. The following 6 indicators were identified: (1) muscle rigidity, (2) muscle breakdown (increased CK level or myoglobinuria), (3) respiratory acidosis or hypercarbia, (4) temperature increase (single hyperthermic episode or a rapid increase in temperature), (5) cardiac involvement (tachyarrhythmia or ventricular arrhythmia), and (6) family history of MH. The raw score from all 6 indicators is tallied from 0 to 50+, and an MH rank from 0 to 6 is totaled (6 being the most likely). In addition, a description of the likelihood of an MH reaction is assigned a phrase with a range from "almost never" to "almost certain." The CGS for MH is a very valuable tool to assist in early MH recognition and is often used in retrospective reviews to confirm the diagnosis. Organizations such as the MHAUS use a similar grading scale when anesthesiologists phone the hotline to discuss a case and decide the likelihood of MH and whether to treat. Because most pediatric presentations are not classic presentations, it is extremely helpful to use the CGS to assist in diagnosis [25].

Historically, temporomandibular joint or masseter spasm occurred in 1% of mask inductions with halothane and succinylcholine. However, these reactions were self-limited and dantrolene was rarely given. Masseter spasm is rarely seen now that halothane and succinylcholine are used less frequently [57]. Often case reports and older studies routinely included masseter spasm as an early clue to an MH reaction, but modern anesthetics do not routinely use either agent so anesthesiologists must be aware of other presenting signs.

In a study done by Nelson and Litman [22] in 2014, using NAMHR data, 351 subjects from 1960 to 2011 were reviewed for MH using the CGS scale and 264 or 75.2% of patients met the criteria for almost-certain MH. The patients were then separated into 3 categories to better define any possible presentation trends among the pediatric population. Thirty-five children were in the youngest (0–24 months) age group, 163 were in the middle (25 months to 12 years) age group, and 66 were in the oldest (13–18 years) age group. The likelihood of the condition being seen in male patients increased with age, and was most pronounced in the oldest group. A family history of MH was present in 18.5% of patients with MH. The MH event occurred with the first anesthetic in 50% of patients and during the second anesthetic in 20% of patients. The investigators hypothesized that earlier recognition of MH might occur if more common presentations per pediatric age group could be identified. Across the entire pediatric range, sinus tachycardia was the first sign of an MH crisis in 73.1% of cases, hypercarbia was seen second in 68.6%, and a rapid temperature increase was seen in 48.5%. The oldest group of patients were most likely to develop all 3 and to reach the highest maximum temperature. It is thus helpful to understand that teenaged patients are more likely to develop classic MH symptoms of tachycardia, hypercarbia, and hyperthermia. The greater muscle mass typically present may explain the more common

classic presentation of MH that is seen in older children. This possibility is further supported by the fact that teenaged patients develop higher peak CK and potassium levels, and a greater degree of rhabdomyolysis, when they have MH. Patients aged 2 to 12 years more typically developed lower peak $ET_{CO_2}$and Pa_{CO_2} but were more likely to show masseter spasm, especially if succinylcholine was used. This middle group (2–12 years) was the most heterogeneous group with regard to presentation. The youngest patients (<2 years) more frequently showed skin mottling, were half as likely to show muscle rigidity, and developed higher peak lactic acid and lower peak CK levels, likely secondary to higher resting metabolic rates and decreased muscle reserve. This study by Nelson and Litman [22] highlights the variety of MH symptoms that can be seen in pediatric MH crisis.

SPECIAL SCENARIOS/DIFFERENTIAL DIAGNOSIS

Despite earlier recognition and better survival among the pediatric population, there are a few special circumstances that any anesthesiologist that cares for children should consider. Brandom and Muldoon [58] in 2013 described multiple fatal pediatric MH cases without exposure to triggering agents. Common elements seen were muscle rigidity; increased temperature; cardiovascular collapse; and, on follow-up review, an abnormal RYR type 1 gene. Some patients with MH without a triggering exposure had a recent viral illness, but that was not uniformly seen. As discussed earlier, the presentation of MH is highly variable in children, and a wide differential diagnosis must be considered even if a nontriggering anesthetic is used. Anesthesia-induced rhabdomyolysis (AIR) should be considered early in the setting of a patient being considered for MH. Both AIR and MH have similar presentations with hyperthermia and muscle rigidity, but the early treatment strategies are different. AIR should be more strongly considered in any patient with a known history of muscle myopathies. Essential treatment of AIR is calcium and cardiovascular support, whereas IV dantrolene is critical in the treatment of MH.

An additional consideration in the future of MH treatment involves earlier recognition of MH with advanced electronic detection and clinical decision support. A group at Mayo Clinic has developed and tested an electronic medical record (EMR) MH detection tool, which they have applied to 10 years of data. Their EMR tool was used to analyze data in a model of the flow in an operating room. The real-time detection device or ''data sniffer'' was reported to be sufficiently sensitive that providers would have been alerted earlier than recognition occurred during the original event [59]. It is a novel approach to MH recognition and treatment that will be explored further in the future.

SUMMARY

MH remains a relevant clinical emergency in anesthesia more than 50 years after its characterization, and 40 years after the development of the antidote drug, dantrolene. Advances in genetic testing and research have yielded vast

amounts of information about the electrochemical processes involved and the genetic mutations responsible for MH events, but contracture testing continues to be a key element in establishing phenotype. The shared goal is vigilance in monitoring and efficiency in treatment that brings mortality from MH to zero.

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