Review Article

A comprehensive review of malignant hyperthermia: Preventing further fatalities in orthopedic surgery

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ARTICLE INFO

Keywords:

Malignant hyperthermia
Malignant hyperpyrexia
RYR1 pathology
Dantrolene
Core myopathy

ABSTRACT

Most frequently associated with orthopedic surgery, malignant hyperthermia is a rare genetic condition linked to volatile anesthetics and succinylcholine. If not treated quickly with appropriate measures, death may result. To aid in the prevention of further fatalities, this review seeks to educate clinicians and staff on the presentation and treatment of this disease, as well as to provide a comprehensive overview by further addressing prevalence, similar conditions, pathogenesis and other aspects. Although the number of deaths due to malignant hyperthermia has greatly declined in the last several years, increased knowledge may eliminate associated mortalities, particularly in the orthopedic setting.

1. Introduction

Malignant hyperthermia (MH) is an autosomal dominant disorder^{1–4} which presents as a hypermetabolic reaction to volatile anesthetics such as halothane, isoflurane, sevoflurane, and desflurane (nitrous oxide and xenon have not been implicated in the disease),^{4,5} as well as the depolarizing muscle relaxant succinylcholine. Exertional heat stroke, exercise-induced stress, infection, emotional stress, and statin therapy are also known to precipitate MH.^{1,4,6} While mortality has improved significantly from approximately 64% in 1980⁷ to estimates of less than 5% in the last decade,⁴ this treatable disease continues to claim lives each year. Therefore, a keen awareness of MH is critical to clinicians and staff involved in any surgical field, particularly orthopedics. The aim of this review is to concisely summarize the causes, incidence, symptoms, mechanism, predisposing factors, treatment, prevention and diagnosis of MH, to serve as an inclusive reference tool for healthcare providers. A critical survey of the literature was performed in PubMed and related journal databases using key words such as: malignant hyperthermia, malignant hyperpyrexia, core myopathies, dantrolene, malignant hyperthermia mutations, RYR1 pathologies, malignant hyperthermia susceptibility predisposition, and contracture testing. No restriction on publication date was used.

2. Discussion

2.1. Incidence and affected populations

MH is thought to be a dose-dependent event dictated by

interindividual variability,⁵ with patients requiring on average three exposures to anesthetics before experiencing a crisis.^{1,4} Although this trend complicates estimates of the true incidence of the disorder, the literature presents a range between 1:10,000 and 1:250,000.^{1,4,6,8,9} Children and young adults are especially at risk, with children under 15 years of age accounting for over half of all cases.^{4,5,8} Further, the mean age of MH patients is 18.3 years.⁴ Of note, the occurrence of MH in the infant population is somewhat unclear; some deny the susceptibility of neonates, while various reports exist of 0–24 month-olds displaying hallmarks of an MH episode.⁸ Overall, males are more often affected than females, as are those with a muscular body build.^{4–6} All races are equally susceptible worldwide.

2.2. Symptoms and similar conditions

Apart from being rare, the difficulty of recognizing an MH crisis is compounded by its variable presentation.^{4,5} However, several key clinical features exist. An early and specific sign of MH is an unexplained rise in end-tidal CO₂ levels with increased ventilation.^{1,4–6} If succinylcholine is used, this rise in CO₂ may be more rapid.¹ Other symptoms include tachycardia and dysrhythmia, an abrupt rise in core body temperature (the rate of change of temperature is more significant than peak temperature),⁵ generalized skeletal muscle rigidity and rhabdomyolysis. With progression of the crisis, respiratory and metabolic acidosis, increased serum potassium, elevated creatine kinase levels, and myoglobinuria may occur.^{1,4–6} Eventually, a patient may suffer from acute renal failure and/or disseminated intravascular coagulation.^{4,5} A summary of the key clinical features is presented in

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Table 1
Key clinical features of malignant hyperthermia.

Presentation	Noteworthy lab values
Increase in end-tidal CO ₂ levels	Respiratory / metabolic acidosis
Tachypnea	Elevated serum potassium
Tachycardia	Elevated creatine kinase
Dysrhythmia	Myoglobinuria
Rise in body temperature	
Muscle rigidity	
Rhabdomyolysis	
Acute renal failure	
Disseminated intravascular coagulation	

Table 1.

Conditions associated with anesthesia which mimic MH include sepsis, surgical stress, inadequate anesthetic depth, transfusion-related issues, isolated master muscle rigidity (MMR), thyrotoxicosis, pheochromocytoma, and iatrogenic overheating.^{1,4} Specifically in children, hypovolemia, allergies, anticholinergic treatments, and disturbances to the CNS may present similarly.¹⁰ Another condition, anesthesia-induced rhabdomyolysis (AIR), is induced by the same agents but requires different management.¹¹ In young males in particular, sudden hyperkalemic cardiac arrest is a syndrome often confused with MH.⁴

2.3. Mechanism of the disease

In a normal individual the neurotransmitter acetylcholine initiates an action potential that propagates along the sarcolemma, or plasma membrane, of a muscle fiber. This action potential reaches the transverse tubules (t-tubules), which are infoldings of the sarcolemma, activating voltage-gated dihydropyridine receptors (DHPRs).^{1,4,5} Consequently, the closely-associated ryanodine receptors subtype 1 (RYR1), predominant in skeletal muscle, open and release calcium from the sarcoplasmic reticulum (SR) into the cytosol, resulting in muscle fiber contraction. Relaxation of the fiber is facilitated by return of calcium to the SR via energy-expending ion pumps (sarco/endoplasmic reticulum Ca²⁺-ATPase, SERCA). The internal structure of a muscle fiber and associated relationship of the calcium-releasing RYR1 are shown in Figs. 1 and 2.

In MH, the liberation of calcium into the cytosol is dysregulated. There is an accelerated release of Ca²⁺ out of the SR for which SERCAs are unable to adequately compensate, causing a disruption in the

Fig. 1. Muscle fiber architecture: The sarcolemma is the unique name given to the plasma membrane of a muscle fiber, with its infoldings known as transverse tubules (t-tubules). Also shown is the relationship of the sarcoplasmic reticulum, from which calcium stores are released with activation of the ryanodine receptor.

Fig. 2. Ryanodine receptor and calcium release: An action potential propagating along the sarcolemma traverses down the transverse tubules (t-tubules), leading to the eventual activation of ryanodine receptors. These receptors release calcium stores held in the sarcoplasmic reticulum, leading to muscle contraction.

management of intracellular calcium levels. Persistent muscular rigidity results, as does increased expenditure of energy in the form of ATP.^{1,4,6} These two factors lead to hypermetabolic activity, giving rise to increased CO₂ levels, heat production (hyperthermia), failure of membrane integrity of muscle fibers (rhabdomyolysis), and eventually hyperkalemia, myoglobinemia, and increased creatine phosphate and creatine kinase.^{1,4-6}

2.4. Predisposition to malignant hyperthermia

Several genetic abnormalities signal a predisposition to MH, which have a reported prevalence of 1:3,000–4,000.⁴ A mutation in the RYR1 locus is currently most correlated with MH susceptibility. Greater than 50–70% of MH families carry such a mutation, with approximately 34 variations functionally linked to the disease and used diagnostically.^{1,4,6} An estimate of two mutations within the main subunit of DHPR (CACNA1S) have also been documented as associated irregularities.^{1,2,4,5} A number of other loci have been suggested as well, although they are not yet definitively linked to MH.^{1,4}

Many core myopathies are also related to mutations in the RYR1 gene, potentially predisposing those with such disorders to MH.^{6,9} Muscle diseases linked to MH include central core disorder, multi-minicore disease, King Denborough syndrome, chronic myopathy, congenital fiber type disproportion, central nuclear myopathy, and exertional rhabdomyolysis.^{1,4,8,9} There is some disagreement surrounding MH susceptibility related to muscular dystrophies, myotonias, and osteogenesis imperfecta.^{1,4,12}

2.5. Treatment and management

In the case of a suspected episode of MH, all triggering agents should immediately be withheld and surgery rapidly aborted; if surgery must be continued, intravenous anesthetics and non-depolarizing muscle relaxants can be used.^{1,5,6} Hyperventilation, cooling of the patient, and administration of dantrolene, an RYR1 antagonist, should occur concurrently.⁴⁻⁶ Dantrolene should be given at a dose of 2–2.5 mg/kg every five minutes until the patient stabilizes.⁴⁻⁶ If more than 10–20 mg/kg of dantrolene is given in total with no improvement, a diagnosis of MH should be reconsidered.^{4,5} Further, dantrolene is not efficacious solely for MH, so control of symptoms with administration does not necessarily confirm MH.⁴ Hyperkalemia and arrhythmia can be treated with standard medications. However, it is crucial to avoid calcium channel blockers, as these will result in cardiac arrest in combination with dantrolene.⁴⁻⁶ It is recommended that blood gas

analysis, blood glucose, electrolyte, lactate, creatine kinase, urine and blood myoglobin, and coagulation studies be evaluated at the onset of MH and repeated at 30 min, 4 h, 12 h, 24 h, and 48 h.⁶

If dantrolene is not readily accessible, successful management of MH may be possible via alternative means, as evidenced in two pediatric cases.¹³ Measures such as dopamine, dobutamine, hydrocortisone, heparin, and furosemide administration, in addition to other supporting therapies, were successfully used.¹³

Although rare, MH may manifest postoperatively in some instances. To enact treatment if necessary, careful monitoring for symptoms for at least 30 min after general anesthesia is recommended.⁶

Recrudescence of MH may also be possible, in which signs of the disorder return after proper treatment of an initial MH episode.^{1,4,14} Approximately 20–25% of patients will experience a recrudescence event.^{1,4} While the mean time from initial reaction to recrudescence has been reported as 13 h, a timeframe of 36–72 h of observation is suggested.^{1,4,14} Factors that may predispose an individual to recrudescence include muscular body habitus, a longer interval between induction and MH reaction, and a temperature increase.¹⁴

2.6. Prevention

To prevent MH events in susceptible individuals, use of intravenous anesthetics is assumed to be safe, as is the administration of local or regional anesthetics.⁶ As such, when non-triggering agents are used, patients do not need to be supervised for several hours after exposure.⁴ However, if these patients are retained in the PACU where ambient volatile anesthesia is present, risk of developing postoperative MH is possible.¹⁵ Although once commonplace, pretreatment with dantrolene is also unnecessary.^{4–6}

Another significant preventative measure, particularly in cases where MH susceptibility is not known, is the use of core temperature monitoring.¹⁶ In a study by Larach et al, death due to MH was 14 times more likely in the absence of core temperature monitoring and 9.7 times more likely when only skin temperature monitoring was utilized.^{4,16} Core temperature monitoring provides a means for more timely and life-saving intervention in the event of MH.

Real-time MH detection tools may represent a future resource for more immediate detection and prevention of progressed MH. In 2016, Gleich et al described an instrument they developed based on well-recognized physiologic criteria capable of detecting possible MH perioperatively.¹⁷ Although further investigation is needed, the demonstrated sensitivity and specificity appeared suitable, enabling it to accurately alert the provider for more expeditious initiation of treatment.¹⁷

2.7. Diagnostic testing

Two main methods exist for identification of MH susceptibility, in vitro contracture testing (IVCT) and DNA analysis. For the past 30 years, IVCT has been the gold standard for diagnosis of MH,^{4,5} with a sensitivity of 97–99% and a specificity of 78–94%^{1,18} depending on the protocol used. In IVCT, MH susceptibility is detected via the response of a sample of skeletal muscle to caffeine or halothane. A major drawback, however, is that testing must be carried out in a qualified center. Additionally, IVCT is an invasive tool, requiring a muscle biopsy. The muscle sample must also be of a particular length and weight, excluding young children and infants as candidates for testing.⁸

Although still dependent upon accredited diagnostic laboratories, DNA screening in patients from MH families is becoming the preferred first line of testing.^{1,4,5,19} Individuals of any age and weight are able to undergo evaluation. Requiring only a blood specimen, whole exome or targeted exon NGS (next-generation sequencing) can be used for variant detection.^{4,5} For identified variants outside the established MH-associated RYR1 and CACNA1A mutations, bioinformatic tools exist for prediction of pathogenicity, although accuracy may vary.⁴ For patients

from MH families without any detected mutations, IVCT can be used to confirm or exclude susceptibility. Importantly, even when the results of both genetic testing and IVCT are negative, MH susceptibility cannot necessarily be ruled out.⁶

Additional less invasive options are under development.

3. Conclusion

Because MH is cited as a complication most often seen in orthopedic surgery,²⁰ it is critical that providers be well-versed in recognizing the signs and symptoms of the disorder, as well as being capable of instituting proper treatment quickly. MH is treatable and fatalities can be further reduced with increased vigilance. For this reason, this review article provides a succinct summary of clinically applicable information to serve as a comprehensive resource on MH for orthopedists and staff.

Authors' contributions

Conception of the work was led by NAE. JLS collected data and drafted the manuscript. MAT critically revised the manuscript and conducted the selection of figures and preparation of the table. All authors approved the final version for publication.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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