MH-associated diseases: who really needs a non-triggering technique?

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Malignant hyperthermia (MH) is a pharmacogenetic clinical syndrome that occurs in patients with preexisting abnormal skeletal muscle. It manifests clinically as a hypermetabolic crisis when a MH-susceptible individual is exposed to an inhalational anesthetic or a depolarizing muscle relaxant (ie, succinylcholine).

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History and incidence

In 1962, Denborough and colleagues described a young man who, while waiting for surgery for his fractured leg, described 10 of his relatives that died without explanation during or following general anesthesia.1 Despite his anesthesiologist’s use of a new anesthetic called halothane, the man developed severe hyperthermia, tachycardia, and tachypnea, and remarkably, survived the event using aggressive cooling. Upon subsequent investigation of the patient’s family, Denborough noted an autosomal dominant pattern of the anesthetic-related illness, and concluded that the susceptibility to this disorder was inherited. Once published, this report stimulated the publication of additional cases of anesthetic-induced hypermetabolism, many of which were accompanied by muscle rigidity, rhabdomyolysis, hyperkalemia, renal failure, disseminated intravascular coagulation (DIC), and death. Over subsequent years, the syndrome became known as malignant hyperthermia (MH), because of its often fatal nature and association with uncontrolled high body temperature. Further investigation showed a predisposition to MH when susceptible patients were exposed to inhalational agents or succinylcholine (and frequently both). Eventually, dantrolene, a nonspecific muscle relaxant that inhibits intracellular calcium accumulation, was shown to be an effective antidote and decreased MH-related mortality from 40% to less than 5%.

The incidence of MH susceptibility has been reported to be as low as 1 in 250,0002 and as high as 1 in 200,3 depending on the geographical region studied. The true prevalence is unknown because of unrecognized or aborted reactions and the variable penetrance of the inherited trait. Furthermore, many MH-susceptible patients may never be exposed to anesthetic triggering agents. Almost all MH-susceptible patients are phenotypically normal and will only manifest the clinical characteristics of MH when exposed to anesthetic triggering agents.

Clinical features

The first signs of an acute MH episode are manifestations of systemic, uncontrolled hypermetabolism during general an-
esthhesia with a triggering agent. Presenting signs may include tachycardia, hypertension, muscle rigidity, and hypercarbia, the last of which reflects an increase in the production of CO₂. The most common initial sign of acute MH is an unexplained rise in end-tidal carbon dioxide that does not readily decrease with increases in minute ventilation. The clinical presentation is not uniform and the time of onset is variable between patients. The presence of masseter muscle spasm following administration of succinylcholine may herald the onset of MH in some patients. Cardiac dysrhythmias, including ventricular tachycardia or fibrillation, may indicate an undiagnosed underlying hyperkalemia as a result of fulminant muscle damage. Localized or generalized muscle rigidity, despite the presence of neuromuscular blockade, indicates a state of unabated muscular contraction, and is strongly indicative of MH when other signs are present.

In cases of known MH, there is wide variability in the interval between exposure to the triggering agent and development of symptoms. The time between onset of initial signs and development of fulminant MH is also variable and unpredictable.

Hyperthermia is a late sign of MH and may not be present at the time of the diagnosis. Hyperthermia is likely caused by continuous muscle contractures that generate more heat than the body can dissipate to the environment. Body temperature can increase at a rate of 1° to 2°C every 5 minutes. Severe hyperthermia (core temperature greater than 44°C) may occur, and can lead to a marked increase in oxygen consumption, CO₂ production, widespread vital organ dysfunction, and disseminated intravascular coagulation (DIC). Prior to the development of hyperthermia, the CO₂ absorbent in the anesthesia machine often becomes warm to the touch as a result of the exothermic reaction with the patient’s exhaled CO₂.

If the hypermetabolism continues unabated, it leads to cellular hypoxia, which is manifested by progressive and worsening metabolic acidosis. If untreated, continued myocyte death and rhabdomyolysis result in life-threatening cellular hypoxia, which is manifested by progressive and worsening metabolic acidosis. If untreated, continued myocyte death and rhabdomyolysis result in life-threatening hyperkalemia, myoglobinuria, renal failure, and DIC.

Once recognized, treatment of MH includes immediate discontinuation of the anesthetic triggering agent and administration of dantrolene sodium. Supportive measures are instituted to reverse the associated hyperthermia, acidosis, hyperkalemia, and to prevent myoglobinuria-induced renal failure.

### Pathophysiology of MH

Malignant hyperthermia susceptibility (MHS) is conferred by inheritance of a mutation of a calcium-regulating structure in the muscle cell, most commonly the ryanodine receptor (RYR1), which resides on the sarcoplasmic reticulum and is responsible for regulating calcium entry into the myocyte. A mutation in the gene for RYR1, which is located on chromosome 19, causes production of an abnormal ryanodine receptor (mutations of other calcium-regulating structures have also been identified). When a MHS patient is exposed to an anesthetic triggering agent, the abnormal ryanodine receptor may remain open for an abnormally long duration, thus allowing too much calcium to be released into the myocyte. The accelerated hypermetabolism, which is characteristic of an acute MH episode, is caused by the overwhelming accumulation of calcium in the muscle cell, thus activating the contractile machinery until the cell uses up ATP, and releases creatine kinase (CK) and potassium into the circulation.

### Diagnosing MH susceptibility

The most widely used and most sensitive method for determining whether an individual is susceptible to MH is the caffeine–halothane contracture test (CHCT). The sensitivity of the CHCT is at least 97%, but in North America, the specificity is lower—up to 22% of patients may have a false-positive test.

Patients with a positive or equivocal CHCT can now undergo molecular genetic analysis to identify a causative mutation. Family members of a proband with an identified MH-causative mutation may also be offered genetic testing without having to undergo a CHCT. Genetic analysis is fairly straightforward, as a DNA sample can be obtained from buccal cells, white blood cells, muscle cells, or other tissue. Molecular genetic testing uses a panel of mutations that includes the most common RYR1 mutations and detects mutations in approximately 25% to 30% of susceptible individuals.

### Relationship between MH and known disease entities

Determining the causation or association of MHS with a particular disease entity is extremely difficult. In considering the chain of credible evidence for determination of causation/association, prospective randomized controlled trials and cohort studies are not feasible, which leaves only case control studies, and case reports and case series. Furthermore, close examination of these published reports reveals a number of problems inherent in the fact that no real gold standard of MHS diagnosis exists (the CHCT has a false-positive rate up to 22%), and definitive diagnosis of specific syndromes is also often in doubt. Most recently, genetic linkage and pedigree analysis studies have furthered the definitive diagnosis of various syndromes and their link to MHS. I will review these diseases as well as the evidence for MHS associated with a number of other diseases.

I think of three types of categories when considering a disease’s link to MHS: 1) those that are definitely linked to MHS by either genetic linkage or overwhelming clinical...
Diseases clearly linked with MHS

Central core disease (CCD)

CCD is a congenital myopathy associated with mutations on the ryanodine gene (RYRI) on chromosome 19, the same gene that harbors many MH-causative mutations. In certain geographical areas of Europe, the prevalence in children is between 3.5 and $5/100,000$. The North American prevalence is unknown. It appears to be inherited in an autosomal dominant manner.

The clinical characteristics of CCD vary between affected individuals, and often consist of motor delay during infancy or early childhood, with a predominance of lower extremity proximal weakness. Secondary musculoskeletal abnormalities may include congenital hip dislocation, foot deformities, scoliosis, and joint contractures. Children with CCD may require general anesthesia for surgical procedures such as gastrostomy tube insertion, muscle biopsy, and correction of orthopedic problems.

Since the clinical features are variable, the diagnosis of CCD is confirmed by the histologic findings of central cores (ie, absence of visible cellular material) within the muscle cells. In most patients, the disease is not debilitating or progressive with age.

It has long been known that many families with CCD also prove to be MHS. This can be explained by the close genetic association (mutations on the same gene that may often overlap) positive MH contracture testing of patients with confirmed CCD, and clinical episodes of anesthesia-associated MH in patients with the disease. There exist some families with CCD that are not MHS; however, in the interest of patient safety relating to administration of general anesthesia, patients with CCD should be treated as if they are also MHS, even without supporting MHS testing.

Multiminicore disease

Multiminicore disease (MMD) is a congenital myopathy inherited in an autosomal recessive fashion. Histologically, the affected muscle tissue demonstrates cores, but unlike CCD, they do not run the entire length of the fiber. Clinically, four subtypes have been identified. The classic, most common type is characterized by limb weakness, scoliosis, and respiratory impairment during early childhood. A second type also includes extracranial muscle impairment. A third type shows prominent proximal lower extremity weakness without the respiratory involvement, and the last type is associated with arthrogryposis.

Like CCD, MMD is caused by a mutation of the RYRI gene, and thus, has overlap with mutations responsible for MHS. Its association with MHS is less than that seen with CCD, but many families have been identified with both, and therefore, patients should be considered MHS until proven otherwise with a negative CHCT.

King–Denborough syndrome/phenotype

The King–Denborough syndrome, or phenotype, is a rare, recessively inherited disorder associated with a consistent set of physical findings that may include short stature, pectus excavatum or carinatum, undescended testicles, subclinical or apparent myopathy (the majority of patients will demonstrate baseline elevated CK levels), ptosis and/or strabismus, and spine abnormalities such as scoliosis. It is often confused with Noonan syndrome, which is similar, but usually has a cardiac component and lacks the myopathic features. A common or consistent genotype has not been identified for King–Denborough patients, but we know that they possess a propensity toward MHS, borne out in both clinical episodes and CHCT analysis.

Diseases with an anesthesia-induced MH-like syndrome

There are many diseases in which triggering agents have caused similar signs and symptoms to MH but the definitive link to MHS is absent. Examples include, but are not limited to, the muscular dystrophies, McArdle’s disease, myoadenylate deaminase deficiency, CPT-2 deficiency, the channelopathies, heat stroke, and exercise-induced rhabdomyolysis.

Muscular dystrophies

The muscular dystrophies encompass a wide variety of myopathic diseases. The most common are Duchenne’s muscular dystrophy (DMD) and Becker’s muscular dystrophy (BMD), both of which have been reported to be associated with MH-like symptoms when affected patients received triggering agents.

DMD is an X-linked recessive disease that usually presents in early childhood as weakness and motor delay. Additional clinical manifestations include pseudohypertrophy of the calves and markedly elevated baseline creatine kinase (CK). Progressive and severe muscle atrophy and weakness cause loss of the ability to ambulate, DMD patients ultimately succumb in early adulthood secondary to a
progressive cardiomyopathy and ventilatory pump insufficiency. DMD is caused by a mutation on the X-chromosome that prevents formation of dystrophin, a muscle-stabilizing protein.22

Despite several case reports of children with DMD that seemingly develop MH,33 no definitive genetic link between DMD and malignant hyperthermia has been found, and many patients with DMD have been exposed to general anesthetic agents without incident. Existing case reports of anesthetic-related complications in DMD patients represent inhalational anesthetic-induced rhabdomyolysis,24-29 succinylcholine-induced hyperkalemia,30-32 or a coincidental inhaled anesthetic-induced rhabdomyolysis.34 There will always be uncommon situations where the benefit-to-risk ratio of using inhalational anesthetics in such patients will be sufficiently high, such as the difficult airway, or impossible intravenous access. In these situations, anesthesiologists should decide, on a case-by-case basis, whether the use of inhalational agents is warranted.

Although many patients with DMD have successfully received inhalational anesthetics without a problem, and DMD does not appear to be linked to MHS, the most prudent and safest recommendation is to avoid their use in children known to be affected with DMD and in boys with a history suspicious for progressive motor delay during early childhood because of the possibility of precipitating rhabdomyolysis.34 There will always be uncommon situations where the benefit-to-risk ratio of using inhalational anesthetics in such patients will be sufficiently high, such as the difficult airway, or impossible intravenous access. In these situations, anesthesiologists should decide, on a case-by-case basis, whether the use of inhalational agents for a short period of time is warranted.

A less severe (yet debilitating) related disease is the Becker-type muscular dystrophy. Similar features to DMD include calf pseudohypertrophy, cardiomyopathy, and elevated serum levels of CPK. However, the onset of weakness in Becker-type dystrophy is later in life than with DMD, and death often occurs at a later age than with DMD. The anesthetic considerations are identical to those for DMD. Succinylcholine-induced hyperkalemia has been reported in a BMD patient.35

Although the dystrophinopathies are not formally associated with MHS, affected patients demonstrate similar signs and symptoms when exposed to triggering agents. Therefore, triggering agents should be avoided in such patients. Furthermore, many pediatric anesthesiologists believe that children with motor delay in the first decade of life should be considered susceptible to these complications and should not receive inhalational anesthetic agents or succinylcholine. Clinical features include muscle cramping, exercise intolerance, and rhabdomyolysis. There is one report of a MHS patient with McArdle’s and numerous reports of patients with McArdle’s that developed perioperative complications including rhabdomyolysis.37,38 Thus, patients with McArdle’s should probably not receive triggering agents.

**Myoadenylate deaminase deficiency**

Myoadenylate deaminase (MAD) is a muscle-specific enzyme involved in the energy metabolism of skeletal muscle. Patients with an inherited deficiency demonstrate exercise intolerance characterized by muscles cramps, elevated CK levels (baseline and increased after exercise), and rhabdomyolysis on occasion. One patient with both MAD and an underlying mitochondrial myopathy was positive for MHS by contracture testing.39 However, there is no additional evidence of its predisposition toward MHS, and thus, patients with MAD deficiency should not be considered MHS; however, it may be prudent to avoid triggering agents in these patients.

**Carnitine palmitoyl transferase type 2 (CPT2) deficiency**

CPT2 deficiency is a type of fatty acid oxidation disorder in which there is abnormal breakdown of fats for energy. It affects both sexes and is inherited in an autosomal recessive manner. Clinical features include muscle weakness or cramps and exercise intolerance associated with rhabdomyolysis. There are a number of reports of patients with CPT2 deficiency who developed perioperative rhabdomyolysis but no definitive link to MHS.40,41 Because of these case reports, CPT2 deficiency should probably be considered in a similar category as the above entities, and thus, triggering agents should be avoided.

**Heat- and exercise-induced rhabdomyolysis**

There have been reports of the association between MHS and rhabdomyolysis or death from heat stroke42 and strenuous exercise.43,44 It has been postulated that MHS patients, by virtue of their underlying muscle abnormality, are predisposed to these complications under stressful conditions, such as extreme heat or exercise. Therefore, patients with a history (or immediate family history) of heat or exercise-induced rhabdomyolysis should probably not receive triggering agents.

**Diseases linked to MHS without evidence**

A number of disease entities have been reported to be linked with MHS. However, in each disease, evidence of MHS or patient harm in association with administration of triggering...
agents is lacking when the case is examined critically. Diseases in this category include Noonan’s syndrome, arthrogryposis, osteogenesis imperfecta, the mitochondrial myopathies, and neuroleptic malignant syndrome (NMS).

Noonan’s syndrome

Noonan’s syndrome is an inherited constellation of anomalies in males that consists of short stature, webbed neck, low set ears, congenital heart disease, pectus excavatum, and varying degrees of developmental delay or mental retardation. It has been loosely associated with MHS; however, there are no convincing case reports or proof of association by contracture testing or genetic mutation analysis. Because of the similarity of features, Noonan’s syndrome has been confused with King–Denborough syndrome, which may explain reports of the association of Noonan’s with MHS. Thus, children with Noonan’s syndrome are not considered to be MHS.

Arthrogryposis

Arthrogryposis is a condition of congenital joint contractures that occurs in a variety of different inherited neurogenic or myogenic syndromes. Affected patients have demonstrated hyperthermia and hypermetabolic responses to general anesthesia, but MH has not been observed with any certainty. Therefore, these patients should not be considered to be MHS.

Osteogenesis imperfecta

MH has been reported in children with osteogenesis imperfecta (OI); however, the diagnoses have not been confirmed by contracture testing or genetic mutation analysis. The clinical diagnosis is further complicated by reports of such children developing non-MH-associated hyperthermia and metabolic acidosis. Until there are more convincing reports or genetic evidence confirming the link between OI and MH, these children should not be considered to be MHS, but should be observed for development of hyperthermia in the perioperative period.

Mitochondrial myopathies

The mitochondrial myopathies are a group of genetic diseases whose origin is a defect in mitochondrial function, causing interference with normal adenosine triphosphate (ATP) production. Although mitochondrial defects can affect almost every organ system, those organs with high metabolic rates—such as the heart, brain, and skeletal muscle—are particularly vulnerable. ATP depletion results in accumulation of lactate, a byproduct of anaerobic metabolism. Clinical manifestations include abnormalities of the heart (eg, cardiomyopathy, conduction defects), skeletal muscle (eg, atrophy, weakness), and central nervous system (eg, seizures, encephalopathy, peripheral neuropathies, ophthalmologic manifestations), among many others. Examples of mitochondrial diseases include chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome, Leigh’s disease, Leber’s hereditary optic neuropathy (LHON), mitochondrial myopathy, and myoclonic epilepsy with lactic acidosis and stroke-like episodes (MELAS syndrome). There is no definitive genetic link between mitochondrial disease and MH susceptibility. In the presence of muscle atrophy, elective use of succinylcholine is contraindicated, as it may cause life-threatening hyperkalemia. Inhalational agents have been used safely in patients with mitochondrial diseases.

Neuroleptic malignant syndrome (NMS)

NMS, which may occur when an individual is exposed to an antipsychotic medication, shares many similarities with MH, including the clinical presentation and treatment (ie, dantrolene). However, no known genetic or causal association exists between MH susceptibility and NMS.

Evaluation of the hypotonic infant

An almost daily dilemma for pediatric anesthesiologists is the hypotonic infant without a definitive diagnosis who presents for a diagnostic muscle biopsy. How does one pick out the infants with the diseases for which administration of inhalational agents is contraindicated? Unfortunately, there is no certain method; however, the approach is relatively straightforward. Diseases that warrant administration of a non-triggering technique include the congenital myopathies central core disease (CCD) and multiminicore disease (MMD), both of which are considered to be lower motor neuron diseases. Yet, in infancy, it is nearly impossible to differentiate these two entities with the myriad other congenital myopathies or congenital dystrophies. In infancy, the most common cause of hypotonia of unknown etiology is likely to be central in origin (ie, upper motor neuron lesion). These can be differentiated from the lower motor neuron diseases by their presence of normal or hyperactive reflexes. Furthermore, infants with central disease often have a depressed level of consciousness, whereas infants with a peripheral myopathy are usually alert and cognitively normal for age. Additional evidence against a diagnosis of CCD or MMD include laboratory evidence characteristic of metabolic diseases (eg, hyperammonemia, lactic acidosis, etc.). However, increased creatine kinase, although diagnostically nonspecific, is associated with diseases that confer MH susceptibility or anesthetic-induced rhabdomyolysis.

Conclusions

Susceptibility of MH has been reported to occur in a wide variety of patients with different diseases. Those with dis-
eases of the muscle warrant close attention, with contracture testing and genetic mutational analysis to determine the true association with MHS. There are only three entities with a convincing link with MHS: central core disease, multiminicore disease, and King-Denborough syndrome. Other muscles diseases, such as the dystrophinopathies, McArdle’s disease, myophosphorylase deficiency, carnitine palmitoyltransferase type 2 (CPT2) deficiency, and heat- or exercise-induced rhabdomyolysis, have all been associated with signs and symptoms similar to acute MH, and therefore, patients with these entities should probably avoid triggering agents. Other patients with diseases purported to be linked with MH, but for which there is no convincing proof, such as Noonan’s syndrome, osteogenesis imperfecta, arthrogryposis, mitochondrial myopathies, and NMS, may continue to safely receive triggering agents when indicated.

References