Management of the Malignant Hyperthermia Patient in Ambulatory Surgery

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Malignant Hyperthermia (MH) is an inherited muscle disorder characterized by hypermetabolism and triggered by potent volatile anesthetics and the depolarizing muscle relaxant succinylcholine. Clinical signs include hypercarbia, tachycardia, hyperthermia and metabolic acidosis due to abnormal calcium homeostasis resulting in runaway hypermetabolism in the skeletal muscle. Rhabdomyolysis can occur along with disseminated intravascular coagulopathy (DIC) and multi-system organ failure. Early reports of mortality in excess of 70% have been reduced to less than 10% by improved monitoring resulting in early detection and treatment with dantrolene. Management of MH has become well-established and availability of non-triggering anesthetics as well as increased dissemination of information to the anesthetic provider community has decreased the risk as well as the fears of MH-affected individuals. However, the increase in outpatient procedures over the past decade, with procedures often performed in ambulatory care settings where emergency equipment and access to immediate laboratory support may be limited, have increased concern about treatment of unexpected MH crises.

HISTORY

One of the earliest references to an MH-like problem was 1929 when the French pathologist Ombredanne[1] reported postoperative pallor and hyperthermia associated with high mortality in children, however this condition was not identified as a genetic trait. In 1960 Australian physicians Denborough and Lovell[2] reported the first case of a familial history of anesthetic deaths during ether administration. The reported patient barely survived a halothane-induced MH episode. In 1969 Canadian physicians Kalow and Britt[3] described a metabolic error of muscle metabolism noted in patients recovered from MH episodes, forming the basis for diagnostic contracture testing. In 1975 Harrison,[4] a South African, described the efficacy of dantrolene in treating porcine MH. This became the foundation for successfully managing a condition that had been termed "the anesthesiologist's nightmare" due to its unexpected nature and high mortality.

INCIDENCE

The incidence of MH is reported to range from 1:4500 to 1:60,000 general anesthetics (geographic variation is related to the gene prevalence). Approximately 50% of MH-susceptible individuals have had a previous triggering anesthetic without developing MH.[5] MH is rare in infants and the incidence decreases after 50 years of age with males more commonly reported than females.[6] The reasons for these variations are not understood.

MH has been clearly associated with Central Core Disease, multiminicore disease, and King or King-Denborough Syndrome. Association with other disorders such as Duchenne Muscular Dystrophy, myotonia, mitochondrial myopathies, sudden infant death syndrome (SIDS), and neuroleptic malignant syndrome (NMS) is controversial. Exercise-induced MH-related death in adults, especially during exposure to hot environments, has been reported.[7,8]

MECHANISM

Exposure to triggering anesthetics (all potent volatile anesthetics and succinylcholine) causes decreased control of intracellular calcium resulting in a release of free unbound ionized Ca++ from storage sites in the skeletal muscle. The calcium pumps attempt to restore homeostasis which results in ATP utilization, increased aerobic and anaerobic metabolism, and a runaway metabolic state. Rigidity occurs when unbound myofibrillar Ca++ approaches the contractile threshold.

CLINICAL PRESENTATION

Onset of clinical signs can be acute and fulminant or delayed. MH can occur at any time during the anesthetic, and has been reported to occur as late as 24 hours postoperatively. Trismus or masseter muscle spasm following inhalation induction and succinylcholine is associated with an approximately 50% incidence of MH diagnosed by contracture testing. Trismus is often not associated with signs of a fulminant MH episode, however patients must be closely observed for evidence of hypermetabolism as well as rhabdomyolysis. The presence of whole body rigidity or signs of hypermetabolism following trismus increase the risk of MH susceptibility as an etiology. Elevation of CK postoperatively to greater than 20,000 has a strong association with a subsequent MH diagnosis.

Clinical signs and symptoms reflect a state of increasing hypermetabolism. The onset of hyperthermia can be delayed. The earliest signs of MH include tachypnea (in the nonparalyzed patient) and increased end-tidal CO_2 levels. Rigidity, masseter or whole body, occurs in about 75% of cases. Signs of increased sympathetic activity include tachycardia, dysrhythmias, sweating and hypertension.

Supportive laboratory tests for confirmation of MH diagnosis include elevated end-tidal CO_2, blood gas analysis showing a mixed respiratory-metabolic acidosis, elevated serum creatine phosphokinase (CK)

postoperatively, elevated serum and urine myoglobin and increased serum K+, Ca++, and lactate (these findings can be very transient).

TREATMENT

Discontinue triggers immediately and hyperventilate with 100% oxygen. IV Dantrolene should be given early and rapidly when MH is suspected. The initial dosage is 2 mg/kg IV, repeated every five minutes to effect or to a maximum of 10 mg/kg (this limit may be exceeded if necessary). After successful treatment, dantrolene is continued at 1 mg/kg IV q 6 hr for 24 to 48 hours to prevent recrudescence of symptoms. Calcium channel blockers should not be given in the presence of dantrolene as myocardial depression has been demonstrated in swine. Symptomatic treatment during an MH episode may include cooling (stop cooling interventions at 38-39 degrees C to avoid post-treatment hypothermia), antiarrhythmics, management of hyperkalemia, mannitol and/or furosemide to induce diuresis (note that mannitol is present in dantrolene) and sodium bicarbonate. Interventions should be guided by blood gas analysis and clinical signs; administration of dantrolene will usually reverse symptoms rapidly. It is critical that all sites where general anesthesia is administered, including ambulatory and oral surgery centers, have adequate dantrolene supplies to treat an adult patient with MH. Several tragic injuries and deaths have occurred due to delay in treatment in these settings.[9]

Table 1 – Conditions that Mimic MH

Fever (without rigidity)	Fever and/or muscle symptoms	Increased End-Tidal CO_2
Thyrotoxicosis	NMS (psych meds)	Faulty equipment
Sepsis	Hypoxic encephalopathy	Tourniquet (children)
Pheochromocytoma	CSF ionic contract agents	Laparoscopic insufflation
Iatrogenic overheating	Cocaine, amphetamine, ecstasy	
Anticholinergic syndrome	Dystrophinopathy	
	Myotonic syndromes	
	Rhabdomyolysis	

ANESTHESIA FOR MH SUSCEPTIBLE (MHS) PATIENTS

Pretreatment with Dantrolene 1.5-2 mg/kg IV prior to induction is no longer recommended. Choose non-triggering anesthetic agents. Safe anesthetic agents include nitrous oxide, etomidate, ketamine, propofol, all narcotics, all local anesthetics, all barbiturates, all benzodiazepines and all non-depolarizing muscle relaxants. Agents used for reversal of muscle relaxants are also safe. Prepare the machine by removing vaporizers (if possible) or taping over the dials and replacing rubber hoses and soda lime. Flush with high flow oxygen (5 L/m) for 10 minutes.

Standard monitors are used with an emphasis on end-tidal CO_2, oxygen saturation, and core temperature (skin monitors may not reflect core changes). Arterial and central venous pressures need be monitored only if indicated by the surgical procedure or the patient's medical condition. Avoidance of perioperative exposures to potential trace-gas contamination (e.g. the recovery room) is not necessary.

AMBULATORY SETTINGS – SPECIAL CONCERNS FOR MANAGING (MHS) PATIENTS

While the overall incidence of MH episodes is low, the increase in the number of anesthetics in ambulatory care settings over the past decade has resulted in some MH-related deaths in patients with undiagnosed MHS.

Such settings must be prepared to identify and treat acute MH events. Several concerns have been identified in the ambulatory setting:

1. Lack of laboratory backup – identifying MH involves evaluation of acid-base status, serum CK and myoglobin levels and other tests. Ambulatory centers usually do not have immediate access to a laboratory for diagnostic testing.
2. Treatment delay – it is advisable to have dantrolene immediately available in all settings where general anesthetics are delivered, however mixing and administering this medication requires additional medical personnel who may not be available in the ambulatory setting.
3. Transfer from the ambulatory center – patients undergoing an MH episode may be hemodynamically unstable, and transport personnel may not be comfortable with continuing dantrolene treatment. Evaluation at a tertiary care center may further delay treatment and result in worsening symptoms.
4. Ambulatory patients and their families may be "lost to followup" and not receive appropriate genetic counseling after an MH episode.

EVALUATION OF SUSCEPTIBILITY

Patients are referred for evaluation for a number of reasons including unexplained intraoperative death in family members, history of adverse anesthetic event (e.g. trismus), perioperative fever, persistently elevated serum creatine phosphokinase (CK) levels, history of rhabdomyolysis, and associated myopathies (e.g. central core disease). A resting level serum CK level is often obtained in patients suspected of being MHS and may be elevated in approximately 70% of affected individuals.

A clinical grading scale has been devised, and while imperfect, it can help determine whether an individual case fits the diagnosis of MH.

The muscle biopsy contracture testing known as either the *caffeine/halothane contracture test* (CHCT) or the *in vitro contracture test* (IVCT) has always been considered the "gold standard" diagnostic test for MH. Freshly excised muscle, usually from the vastus lateralis or gracilis, is dissected into strips which are mounted in baths and tested with caffeine and halothane alone or in combination; contracture responses are measured

Table 2. Criteria Used in the Clinical Grading Scale for Malignant Hyperthermia (MH)

Process	Clinical Criteria	Points
Muscle rigidity	Generalized rigidity Masseter muscle rigidity	15 15
Muscle breakdown	Creatine kinase > 10,000 units/l Cola-colored urine Excess myoglobin in urine or serum K+ > 6 mEq/l	15 5 3
Respiratory acidosis	End-tidal CO_2 > 55 mmHg; $PaCO_2$ > 60 mmHg Inappropriate tachypnea	15 10
Temperature increase	Rapidly increasing temperature Inappropriate temperature > 38.8°C	15 10
Cardiac involvement	Unexplained sinus tachycardia, ventricular tachycardiac, or ventricular fibrillation	3
Family history	MH history in first-degree relative MH history in family, not first-degree relative	15 5

Only the highest score in any one process should be used when more than one event or sign occurs in a process. The more criteria that a patient fulfills, the more likely that an MH episode has occurred. If only one criterion is fulfilled, then malignant hyperthermia is not likely, whereas malignant hyperthermia is almost certain if all criterial are fulfilled. Other criteria to consider include base excess > -8 mEq/L (10 points), pH < 7.25 (10 points), and rapid reversal of malignant hyperthermia signs with dantrolene therapy (5 points). The likelihood according to point score: 0, almost never; 3-9, unlikely; 10-19, somewhat less than likely; 20-34, somewhat greater than likely; 35-49, very likely; ≥ 50, almost certain. Adapted from Larach et al,[10,11] with permission.

and interpreted according to standardized values. Testing centers in North America have been reduced to five due to several factors including reluctance of insurance companies to pay for the expense of surgery and testing and increased availability of genetic testing. Contracture testing cannot be done on children under 5 years or under 20 Kg weight.

MOLECULAR GENETICS

MH is an autosomal dominant trait; therefore, patients with this condition will have inherited it from at least one parent. However, it is quite common for neither parent to have shown signs of MH either because they have not been exposed to triggering anesthesia or because they did not react.

Two MHS-causative genes have been identified: **RYR1** (MHS1 locus) and **CACNA1S** (MHS5 locus).[12] **RYR1** encodes the type 1 ryanodine receptor of skeletal muscle and mutations of this gene are identified in up to 70-80% of individuals with confirmed MH and in patients with Central Core Disease (CCD). More than 180 mutations in **RYR1** have been associated with MH or CCD, with over half appearing in only one or a few families. **CACNA1S** encodes the α1-subunit of the skeletal muscle dihydropyridine receptor L-type calcium channel. Mutations in this gene account for about 1% of all MHS (2 gene mutations identified). Three additional loci have been mapped, but the genes have not been identified: MHS2, MHS4 and MHS6.

Patients must be carefully selected for genetic testing in order to maximize sensitivity. Usually this means either a positive muscle contracture test or strongly suggestive family or clinical histories for MH. In these cases, complete sequence analysis of the entire **RYR1** coding region increases the detection rate to 70-80%. Linkage analysis for all MHS loci is considered in families with multi-generational (at least two) unequivocal MH diagnosis in 10 family members or more. Discordance between contracture testing and molecular genetic testing is observed in up to 10% of individuals.

MHAUS

The Malignant Hyperthermia Association of the United States (MHAUS) is an active organization which provides support for patients and physicians. Their website found at www.MHAUS.org provides resources for patients, families, and medical providers. MHAUS also sponsors a 24-hour hotline for providing assistance to physicians who are managing MH susceptible patients or treating acute MH episodes.

MH HOTLINE

USA and Canada
1 (800) 644-9737 • 1-800-MH HYPER

Outside the US • 0011 315 464 7079

Also associated with MHAUS is the North American MH Registry, situated in Pittsburgh, PA. Information about MH episodes (via the American Medical Record Association AMRA report) and testing is stored in the Registry where it is available for approved research and reporting.

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