Malignant Hyperthermia - An Update

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History of MH

Early historical descriptions of conditions consistent with the diagnosis of malignant hyperthermia (MH) can be found in the literature. For example, in 1929 a French pathologist described postoperative pallor and hyperthermia associated with high mortality in children. However, his findings were not linked with a genetic trait. It was not until 1960 that Denborough and Lovell reported the first case of a familial history of anesthetic deaths during general anesthesia.[1] A young man with a tibial fracture requiring open reduction expressed great fear concerning ether anesthesia due to ten deaths in family members during surgery. He received the new (at that time) anesthetic halothane, developed fulminant MH, and survived with symptomatic therapy. In retrospect, his survival was fortuitous, since the mortality of fulminant MH without dantrolene treatment was approximately 80 percent!

In 1969, Kalow and Britt[2] studied a small community in Wisconsin which had an unusually high number of anesthetic related deaths associated with high temperatures. They reported a metabolic error of muscle metabolism observed in patients who had recovered from MH episodes. This discovery formed the basis of diagnostic contracture testing, still the "gold standard" for MH diagnosis.

It was not until 1975 that Harrison,[3] a South African researcher, reported the efficacy of dantrolene in treating porcine MH. Dantrolene was approved by the FDA in the early 1980s and is the mainstay in MH treatment. Its efficacy when given early was demonstrated in a 1982 review of MH cases in the United States by Kolb et al.[4]

Incidence and Mortality

Malignant Hyperthermia is an inherited disorder of skeletal muscle affecting humans and certain strains of swine, dogs, horses and other animals. The incidence of MH is reported to range from 1:4,500 (when succinylcholine is used) to 1:60,000 anesthetics. The incidence varies depending on the prevalence of the gene(s) for MH in any given geographic area (e.g. higher incidence in Marathon County, Wisconsin). Malignant Hyperthermia is reported worldwide and affects all racial groups.

Malignant Hyperthermia is rare in infants and the incidence decreases after 50 years of age. Most cases occur in children and young adults and males are more frequently affected than females, although this may be related to other demographic factors. Neonatal piglets were shown to have a lower frequency of halothane-triggered MH compared with four week and older piglets in both *in vivo* and *in vitro* (muscle strips) studies.[5] The mechanism for this age-related difference in sensitivity is not understood.

Malignant Hyperthermia is clearly associated with central core disease and is reportedly associated with certain myopathic disorders such as Duchenne's muscular dystrophy and King Denborough Syndrome. Association with other muscular defects, sudden infant death syndrome, neuroleptic malignant syndrome and sudden death in adults is controversial.[6]

The mortality before the use of dantrolene was approximately 80 % but, in recent years, this has decreased to about 10 %. Most fatal cases are either extremely fulminant in nature or are diagnosed too late for dantrolene to be effective. Unfortunately, many hospitals still do not stock intravenous dantrolene, citing cost factors or sharing a supply with other regional centers, resulting in inadequate doses in both hospitals. This is especially a problem for free-standing ambulatory centers and office-based practices.

Approximately 50 % of MH-susceptible individuals have had a previous triggering anesthetic without developing MH.[7] There could be a number of explanations for this phenomena including cool ambient temperatures in the operating room, use of non-triggering agents which delay the onset of MH, such as sodium pentothal, opioids or nondepolarizing muscle relaxants, and short anesthetic exposure. All of these factors have been shown to prevent or delay MH triggering in the animal model.[8,9] There also may be variable gene penetrance affecting individual responses and other undetermined genetic or environmental factors.[10,11]

Genetics of MH

Most human families show an autosomal dominant pattern of inheritance with variable expression. MH-susceptible swine

have an autosomal recessive pattern. The rate of spontaneous mutation is unknown, and studies of large MH affected populations indicate that more than one chromosome is involved, perhaps explaining the variable clinical expression of the trait.[11]

Initial reports by Maclennan et al[12] and others identifying a specific base pair alteration in the swine gene encoding the ryanodine receptor protein DNA linkage analysis, raised the hope that a specific DNA test would be available for diagnosing human MH.[12,13] Unfortunately, the swine mutation is present in less than five percent of human families.[14] Several mutations (over 20 by a recent count) have been demonstrated on chromosome 19 in humans, some affecting only one family and, taken together, still fail to account for the majority of MH affected individuals. Other chromosomes have also been identified as possible mutation sites in humans including 17, 1, 3, and 7. While this is somewhat discouraging, it is not really surprising when the clinical variability of the condition and the complexity of intracellular calcium control are considered.

In summary, MH is a *heterogeneous genetic disorder* with a highly variable clinical presentation. Hence, the prospect of a clinically applicable DNA test for MH is unlikely.

Clinical Presentation

Malignant Hyperthermia is characterized by a hypermetabolic response to triggering anesthetic agents. While the reaction can be variable in onset and severity, increased CO_2 production, elevated oxygen consumption, acid-base disturbance and muscle breakdown will be present to some degree.

The onset can be acute and fulminant or delayed and covert. Malignant Hyperthermia can occur at any time during the anesthetic, and has been reported to occur as late as 24 h postoperatively. A subacute episode may regress with discontinuation of the anesthetic. However, treatment with dantrolene is advised since recrudescence can theoretically occur.

Trismus following succinylcholine is seen less frequently now that this agent is used in children only when indicated. Trismus or masseter muscle rigidity (MMR) is associated with MH in 50 % of patients undergoing contracture testing.[15-17] While trismus is often not associated with signs of a fulminant MH episode, these patients must be closely observed for evidence of hypermetabolism as well as rhabdomyolysis, which can be severe. Reports of safely continuing triggering anesthesia following trismus are interesting, but the risk of developing fulminant MH following this response should not be underestimated. In general, such practices are to be discouraged.

The rare occurrence of life-threatening hyperkalemia in young males with undiagnosed Duchenne's muscular dystrophy led to the 1992 FDA recommendation that succinylcholine be avoided in children unless specifically indicated. Duchenne's muscular dystrophy occurs in 1 in 3,500 live male births and occasionally is diagnosed as late as 6 to 8 years of age. When cardiac arrest occurs following the administration of succinylcholine in a male child, hyperkalemia should be assumed and treated along with MH. If possible, a muscle sample should be collected for histologic examination including dystrophin levels.[18]

Masseter Muscle Rigidity can also be seen in adults, although it is usually associated with an inhalation induction followed by succinylcholine. Follow-up should include serial creatine kinase (CK) levels every 6 h for 24 h. There is a high correlation with subsequent positive muscle contracture testing when the peak CK (usually at 12-18 h) exceeds 20,000 IU/L.[19] These patients can have significant rhabdomyolysis with elevated urine and serum myoglobin levels requiring treatment to avoid renal complications. Administration of dantrolene is controversial in cases where signs of MH are absent.

Clinical signs and symptoms of MH reflect a state of highly increased metabolism (Table 1). Elevation of temperature is often delayed. The earliest signs of MH include increased $P_{ET}CO_2$, tachycardia, and tachypnea. Laboratory testing is essential in confirming the diagnosis (Table 2). While an arterial blood gas will usually be sufficient, comparison of arterial and mixed venous gases is preferred, since the mixed venous sample will reflect muscle effluent and will give an earlier indication of the metabolic abnormality. Oxygen consumption and cardiac output are initially increased in a healthy individual due to the increased metabolic rate. In an untreated episode, the process will eventually outpace the system's ability to compensate and cardiac arrest with subsequent organ failure will result.

Table 1: Malignant Hyperthermia - Clinical signs and symptoms

Elevated $P_{ET}CO_2$	Sympathetic hyperactivity:
Tachypnea	tachycardia
Muscle rigidity	dysrhythmias
Rhabdomyolysis	sweating
Hyperthermia	hypertension
Late complications:	
muscle edema	
cerebral edema	
cardiac arrest	
renal failure	

Other conditions can mimic MH when hypermetabolism is the underlying mechanism. These include pheochromocytoma, hyperthyroidism, cocaine intoxication and sepsis. The action of dantrolene is not well understood and response to treatment alone will not necessarily differentiate between these conditions and MH. Careful analysis of clinical signs

and laboratory test results will usually help sort out the underlying diagnosis, although this is sometimes best done after the episode has been treated and the patient is clinically stable.

Table 2: Supportive Laboratory Tests for Confirmation of MH Diagnosis

Blood gas analysis
mixed venous vs arterial
Serum Creatine Kinase (CK)
q 6 h for 24 h
Myoglobin - serum and urine
Serum K^+, Ca^{++}, lactate
PT, aPTT, fibrin split products (FSP)

Triggers

An acute MH episode depends on three variables: 1) a genetic predisposition, 2) presence of a triggering agent, and 3) absence or overriding of inhibitory factors. The only anesthetic agents known to trigger MH are the potent inhaled agents (including sevoflurane and desflurane) and succinylcholine.

Safe anesthetic agents include nitrous oxide, etomidate, ketamine, propofol, and all opioids, barbiturates, local anesthetics and nondepolarizing muscle relaxants (Table 3). Controversy about the use of catecholamines in MH-susceptible individuals has been resolved, and these agents may also be included in management of these patients.[20]

Table 3: Safe Anesthetic Agents and Resuscitative Drugs for MH-Susceptible Individuals

- Barbiturates
- Opioids
- Etomidate
- Propofol
- Ketamine
- Nondepolarizing muscle relaxants
- Nitrous oxide
- Local anesthetics
- Epinephrine/Norepinephrine

Pathophysiology of MH

Decreased control of intracellular calcium resulting in uninhibited release of free unbound ionized Ca^{++} from storage sites appears to be the etiology of this condition in affected swine and humans. Intracellular calcium is primarily controlled by the sarcoplasmic reticulum. This site, and more specifically the ryanodine receptor, have been extensively studied in an attempt to identify the mechanism of MH triggering more accurately. However, the varied clinical syndrome and complex genetic inheritance suggest that a simple solution is unlikely. More recently, the role of second messengers and modulators of calcium release have been implicated. There is also some evidence that the sodium channel may play a role in the pathophysiology of MH.

Treatment

A treatment plan for MH should be available wherever general anesthesia is delivered. It is helpful to have an MH cart in a central accessible area (e.g. the recovery room) which contains dantrolene, sterile water for mixing, blood gas kits, resuscitation drugs and other items such as laboratory order forms and an MH protocol. Discontinue triggers and hyperventilate with oxygen 100 % while instituting symptomatic treatment (Table 4). Dantrolene should be given early and rapidly when MH is suspected. The initial dosage is 2.5 mg/kg and can be repeated as needed until signs of MH abate. A total dose of 10 mg/kg is recommended, although this dose can be exceeded safely.[21] However, if the patient does not respond after receiving this dose, alternative diagnoses should be considered. Caution should be taken to avoid overcooling the patient. Administration of dantrolene will usually promptly decrease the core temperature, so external cooling efforts must be monitored closely.

Dantrolene is a hydantoin derivative which is very safe when administered intravenously in the recommended dosages.[22-25] Side effects include nausea, malaise, light headedness, muscle weakness, and irritation at the site of administration due to the high pH of the drug. Muscle weakness is usually peripheral and does not significantly affect respiration, although it may be a problem in newborns or debilitated patients. If possible, dantrolene should be avoided during labor and delivery. Dantrolene contains a large amount of mannitol, a fact that should be taken into consideration when treating the patient with diuretics.

Following successful treatment, 1 mg/kg dantrolene *iv* every 6 h for 24 h is recommended. The patient should be observed with appropriate laboratory testing for at least 24 to 48 h following an MH episode. Potassium salts have been reported to retrigger MH. Calcium channel blockers should not be given in the presence of dantrolene due to the risk of life-threatening hyperkalemia.

Once the patient is stable, genetic counseling should be offered to the family. Materials describing MH, contracture testing, safe anesthetic management in the operating room and the dental office, and patient support information are available from the Malignant Hyperthermia Association of the United States (MHAUS). The medical records should be clearly marked to avoid future exposures to triggering anesthetics and the patient instructed to wear a medic alert bracelet or tag indicating susceptibility to MH. It is especially important to clarify the familial nature of this problem to the patient and immediate family so that the

information regarding the reaction can be disseminated to other family members.

Table 4: Symptomatic Treatment of MH

Cooling
Surface (ice, cooling blanket)
Central
Intravenous iced saline
Nasogastric and rectal lavage
Intraabdominal lavage
Cardiac bypass
Sodium Bicarbonate for metabolic acidosis
Antiarrhythmics
Management of hyperkalemia - insulin/glucose
Diuretics - mannitol, lasix
(dantrolene contains 3 g mannitol per bottle)

Anesthesia for MH Susceptible Patients

Pretreatment with intravenous dantrolene is no longer recommended prior to induction of anesthesia. Non-triggering anesthesia without pretreatment has not been associated with MH episodes.

Machine preparation can be accomplished by removing or completely draining all vaporizers, replacing rubber hoses and soda lime, and flushing with high flow oxygen or air (10 L/min) for 10 min. If vaporizers are drained and left in place, the dial should be securely taped as a reminder that inhalation agents should not be delivered.

The standard intraoperative monitors are recommended including end-tidal CO_2 and core temperature in all patients.[26] Arterial and central venous monitoring are added as indicated by the surgical procedure or medical condition.

Regional anesthesia is a good alternative when appropriate to the procedure and all local anesthetics are safe.

Avoid exposure to potential contamination in the recovery room by isolating the patient or by recovering in the operating room and sending the patient directly to the ward.

Malignant Hyperthermia susceptible patients can be managed as outpatients as long as the usual precautions are observed. Ambulatory centers should have dantrolene available in dosages sufficient to treat a fulminant episode in an adult. Postoperative observation can be managed according to the hospital protocol.

Evaluation of Susceptibility

A patient presenting with a diagnosis of possible MH susceptibility should be carefully questioned regarding unexplained intraoperative deaths in family members, unexpected adverse events under anesthesia, heat stroke or heat intolerance, exercise-induced rhabdomyolysis, associated myopathies, minor muscle abnormalities such as ptosis, strabismus, scoliosis, etc. and a family or personal history of heavy musculature or muscle cramping.

Serum CKs are nonspecific and insensitive, however the CK may be elevated in 70 % of MH susceptible individuals and is often consistent within a given family. This test should be done witrh the subject fasting and in the absence of recent muscle trauma.

Contracture testing with halothane or caffeine on fresh muscle from the vastus lateralis is the only test presently available for diagnosis of MH susceptibility. The sensitivity is > 95% and specificity is 80-85 %. The biopsy must be performed at a biopsy center, of which there are only seven in North America. The North American biopsy centers have agreed to a standardized protocol. Muscle from MH susceptible individuals is more sensitive to caffeine and develops larger contractures to halothane and ryanodine than that of normal individuals. The addition of ryanodine contracture responses appears to add further sensitivity to the testing. The North American Malignant Hyperthermia Registry was created as a repository for patient and control data, and is supported by the North American biopsy centers, general donations and MHAUS.

A number of tests for MH susceptibility have been proposed over the years that remain unstandardized and unconfirmed. These include histologic examination of muscle without contracture testing, electromyography, skinned fiber testing, platelet ATP depletion, and Ca^{++} uptake from muscle strips.

MH information

The Malignant Hyperthermia Association of the United States (MHAUS) is a lay organization providing support for patients, physicians and other health care providers. It publishes books, pamphlets and a quarterly newsletter at nominal costs, and sponsors a 24-h hotline for providing assistance to physicians treating acute MH episodes.

Malignant Hyperthermia Association of the United States
32 South Main Street
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Sherburne, NY 13815
Phone 1-800-98-MHAUS

A fax-on-demand system has recently been introduced: 1-800-440-9990. The MH-hotline number is: 1-800-MH-HYPER. Current information on MH is available on the Internet http://www.mhaus.org.

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