Malignant Hyperthermia: A Review
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Since its first formal description by Drs. Denborough and Lovell of Australia in 1960, malignant hyperthermia (MH) had become one of the most enigmatic genetic disorders affecting general anesthesia until a greater understanding of its molecular and clinical behavior was discerned in the mid to late 1970's.

Malignant Hyperthermia is a rare, fulminant, life-threatening disease referred to as a “syndrome” which occurs during general anesthesia in individuals that have the malignant Hyperthermia susceptibility (MHS) trait and is associated with a rapidly increasing temperature and a high mortality rate if not quickly recognized and treated. Classically, MH develops when specific triggering factors are exposed to genetically susceptible individuals. MH is characterized by hypermetabolism indicated by an increase in CO₂ (carbon dioxide) output, an increase in acid content of the blood, intense muscle rigidity and a rapidly developing fever. In addition, many MH cases have had no genetic susceptibility and have been attributed to stress.

Due to the inherited condition of the MHS trait, patients remain at risk to develop MH throughout their life span. MH has no racial preferences although European Caucasians are most often affected. The mortality rate has decreased from 80% from the time of its original description to less than 10%. The range of affected individuals ranges from age 5 - 72 years with a mean age of 15 years. Males and Females can both be affected but there is a small preponderance towards males being affected 1.5 times more for every one female. There are about 200 cases reported to the MHAUS per year, and the incidence is about 1 in every 16,000 anesthetics. There are certain muscle diseases which have been associated with MH. These include Duchenne Dystrophy, Central Core Disease, Neuroleptic Malignant Syndrome, Myotonia Congenita, King-Denborough Syndrome, Schwartz-Jampel Syndrome and Osteogenesis Imperfecta.

Genetically, MHS was initially described as having an autosomal dominant pattern of inheritance with variable penetrance. However, several genetic loci have been identified discounting this possibility. The gene for the MHS was been located on the human chromosome 19, which encodes the cytoplasmic domain of the skeletal muscle release channel known as the ryanodine receptor (RYR1). Several point mutations linked at this RYR1 gene are considered mostly responsible for being responsible in the development of MH cases. It must be emphasized that not everybody with the MH gene develops an MH episode during anesthesia even if triggering agents are used. There appears to be also the needs to have other factors which might be necessary to experience the episode such as excessive preoperative stress, combination of drugs or length of anesthesia.

The pathophysiology of malignant hyperthermia is a subclinical myopathy in which there is a loss of intracellular calcium ions (Ca²⁺). Malignant hyperthermia trait alters the way the muscle releases and stores its calcium. The event occurs due to exposure of triggering agents which include paralyzing agents mainly succinylcholine and all volatile anesthetic agents such as halothane, isoflurane, enfurane, etc.

At a molecular level, calcium controls the beginning and termination of muscle contraction. The disease is a self-perpetuating, hypercatabolic state due to a defect in release of calcium in the sarcolemma which is not self-limiting. In turn the excess calcium causes persistent contracture of the muscle, excessive activation of ATPase and hydrolysis of adenosine triphosphate (ATP) resulting in depletion of ATP, creatine phosphate (CP), and activation of the ATP-regulating mechanisms with glycogenolysis. Sympathetic hyperactivity (tachycardia, hypertension, increase sweating, etc.) occurs early in the process. Energy production becomes insufficient and the integrity of the muscle breaks down releasing myoglobin and creatine kinase (CK or CPK) into the bloodstream. This will in turn cause a cola-colored urine with possible significant kidney damage. Increase serum potassium (K⁺) results. The MH process may occur within a short period of time (e.g. 15 minutes) or it can take over hours to develop. Cyanosis, skin mottling and hypotension are late signs of the disease along with disseminated intravascular coagulation (DIC.)

The most widely accepted test for determining MH susceptibility is the halothane-caffeine contracture and ryanodine test. This test is performed on living muscle tissue strips. The human muscle is immersed in a liquid chamber where it is exposed to the anesthetic halothane and the drug caffeine. The test uses a protocol with several incremental concentrations of caffeine and uses a 3% halothane bolus application. The contracture test with 4-chloro-m-cresol may add precision. These tests are performed only in limited tests centers in the United States including the ryanodine blood test. Once an individual has been diagnosed with MHS, DNA mutations testing should be performed. Relatives should also receive testing and counseling. For further information about the test can be found in the North American Testing Protocol (CHCT) of the MHAUS Registry.

Dantrolene sodium (Dantrium®), the main pharmacological therapeutic, is packaged in 20mg bottles with NaOH (sodium hydroxide) for a pH of 9-10 to allow dissolution of the drug. In addition, 3g of mannitol is added to convert the hypotonic solution into an isotonic solution. The drug needs to be dissolved in sterile water only and not with other type of fluids since sterile water enhances its quick dissolution. The drug is produced only by Procter & Gamble Pharmaceuticals. The shelf life is about three years. Cost is $82.00 per vial and up to 36 vials might be required for a full blown MH episode. Dantrolene is a calcium channel blocker, has a half-life of at least 10 hours, and does not paralyze muscle but does cause some muscle weakness which is accentuated in myopathic patients.

Treatment of an MH episode starts by:

1.- Discontinuation of all triggering agents and administration of 100% oxygen and hyperventilation of the patient. This helps compensate for the excessive need of oxygen being consumed and to also remove the high levels of CO₂ from the blood.
2. Change of the anesthetic circuit and flushing of the machine should also be performed. Surgery should be finished as quickly as possible.

3. Dantrolene should be given at repeated doses of 2mg/kg every 5 minutes up to a total dose of 10mg/kg.

4. Control fever by use of ice fluids, surface cooling and cooling of body cavities with sterile ice fluids if one is able to. Cooling should be halted at 38°C - 39°C to prevent inadvertent hypothermia.

5. Administer bicarbonate 2-4 mEq/kg to control the lactic acidosis caused by the efflux of lactate from skeletal muscle to the extracellular fluid.

6. Transport of the patient to the hospital is required and admission to the intensive care unit (ICU) is highly recommended. The progression of the clinical picture needs to be monitored aggressively and extensively. These include monitoring urinary output to prevent shock from the kidneys, acute tubular necrosis and myoglobinuria.

7. Analyze electrolytes especially potassium (K+), CK concentrations, liver profile, levels of blood urea nitrogen (BUN), lactate, glucose, coagulation studies (i.e. INR, platelet count, prothrombin time (PT), fibrinogen, fibrin split or degradation products), serum and urine hemoglobin and myoglobin.

8. Further therapy is guided by the clinical course of blood gases, electrolytes, temperature, dysrhythmias, muscle tone and urinary output.

Recrudescence of MH approaches 50% usually within 6.5 hours. Early diagnosis and appropriate treatment with dantrolene are the hallmark of successfully treat MH. Dantrolene markedly attenuates loss of calcium from the SR, restoring metabolism to normal with reversal of the signs of metabolic stimulation.

Anesthesia for MH susceptible patients should consists of nitrous oxide, barbiturates, etomidate, propofol, opiates, tranquilizers and nondepolarizing muscle relaxants. Succinylcholine and all inhalation anesthetics (halothane, enflurane, isoflurane, sevoflurane, desflurane, ether) are to be avoided. Aerate anesthesia machine by removing vaporizers and circuitry and carbon dioxide absorbent canisters. Monitoring should include ECG, end tidal CO2 (capnography), pulse oximetry, blood pressure and core temperature via either rectal or esophageal thermometer. Liquid crystal display of skin temperature or axillary temperature are inadequate because during an MH episode there may be cutaneous vasoconstriction preventing skin temperature from increasing along with the core temperature. As always, observation of skin color, pupils, muscle tone and jaw tension can provide early signs of an MH episode. Prophylactic use of dantrolene is controversial. Currently, recommendations are NOT to use dantrolene prophylactically. Finally, regional anesthetic techniques can be used to provide profound anesthesia in MH susceptible patients.

Education, training, preparedness and vigilance should always be part of understanding and proper treatment of any MH episode for a positive outcome. The author strongly encourages doctors to become very familiar with this pathological entity if anyone is currently using or are considering the use of volatile anesthetic agents. The Malignant Hyperthermia Association of the United States (MHAUS) has produced educational kits for patients and doctors. It is a non-profit organization which was founded in 1981 and is dedicated to help MH susceptible families in any way possible. In addition they sponsor many services for families and have created the MH registry in 1987 to acquire, analyze and disseminate patient-specific clinical laboratory information on malignant hyperthermia susceptibility. Their address and telephone number is: MHAUS - P.O. Box 191 Westport, CT 06881-0191 Tel. (203) 655-3007.

REFERENCES

1.- Malignant Hyperthermia Association of the United States (MHAUS). Understanding Malignant Hyperthermia. 2nd Ed. 1992, Pg. 5.


7.- Malignant Hyperthermia Association of the United States (MHAUS). Understanding Malignant Hyperthermia. 2nd Ed. 1992, Pg. 16.


