Malignant hyperthermia (MH)

Malignant hyperthermia (MH) or malignant hyperpyrexia is a rare life-threatening condition that is usually triggered by exposure to certain drugs used for general anesthesia, specifically the volatile anesthetic agents and the neuromuscular blocking agent, succinylcholine. In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated quickly.

Susceptibility to MH is often inherited as an autosomal dominant disorder, for which there are at least 6 genetic loci of interest, most prominently the ryanodine receptor gene (*RYR1*). MH susceptibility is phenotypically and genetically related to central core disease (CCD), an autosomal dominant disorder characterized both by MH symptoms and myopathy. MH is usually revealed by anesthesia, or when a family member develops the symptoms. There is no simple, straightforward test to diagnose the condition. When MH develops during a procedure, treatment with dantrolene sodium is usually initiated; dantrolene and the avoidance of inhaled anesthesia in susceptible people have markedly reduced the mortality from this condition.

Classification

This condition is known by a number of names, including malignant hyperthermia (MH), malignant hyperthermia syndrome (MHS), malignant hyperthermia susceptibility (MHS), and malignant hyperpyrexia.[1]

Signs and symptoms

The typical symptoms of malignant hyperthermia are due to a hypercatabolic state, which presents as a very high temperature, an increased heart rate and breathing rate, increased carbon dioxide production, increased oxygen consumption, acidosis, rigid muscles, and rhabdomyolysis.

The symptoms usually develop within one hour after exposure to trigger substances, but may even occur several hours later in rare instances.

Causes

Malignant hyperthermia is a disorder that can be considered a gene-environment interaction. In most people with malignant hyperthermia susceptibility, they have few or no symptoms unless they are exposed to a triggering agent. The most common triggering agents are volatile anesthetic gases, such as halothane, sevoflurane, desflurane, isoflurane, enflurane or the depolarizing muscle relaxants suxamethonium and decamethonium used primarily in general anesthesia. Other drugs that have been suspected of causing MH include catecholamines, phenothiazines, and monoamine oxidase inhibitors. There are also few reports of MH being triggered by nitrous oxide administration. In rare cases, the biological stresses of physical exercise or heat may be the trigger.

Other anesthetic drugs are considered safe. These include local anesthetics (lidocaine, bupivacaine, mepivacaine), opiates (morphine, fentanyl), ketamine, barbiturates, nitrous oxide, propofol, etomidate, benzodiazepines.

The nondepolarizing muscle relaxants pancuronium, cisatracurium, atracurium, mivacurium, vecuronium and rocuronium also do not cause MH.

There is mounting evidence that some individuals with malignant hyperthermia susceptibility may develop MH with exercise and/or on exposure to hot environments.

Genetics

Malignant hyperthermia's inheritance is autosomal dominant. The defect is typically located on the long arm of chromosome 19 (19q13.1) involving the ryanodine receptor. More than 25 different mutations in this gene are linked with malignant hyperthermia. These mutations tend to cluster in one of three domains within the protein, designated MH1-3. MH1 and MH2 are located in the N-terminus of the protein, which interacts with L-type calcium channels and Ca^{2+}. MH3 is located in the transmembrane forming C-terminus. This region is important for allowing Ca^{2+} passage through the protein following opening.

Chromosome 7q and chromosome 17 have also been implicated. It has also been postulated that MH and central core disease may be allelic and thus can be co-inherited.

Pathophysiology

Disease mechanism

In a large proportion (50–70%) of cases, the propensity for malignant hyperthermia is due to a mutation of the ryanodine receptor (type 1), located on the sarcoplasmic reticulum (SR), the organelle within skeletal muscle cells that stores calcium. RYR1 opens in response to increases in intracellular Ca^{2+} level mediated by L-type calcium channels, thereby resulting in a drastic increase in intracellular calcium levels and muscle contraction. RYR1 has two sites believed to be important for reacting to changing Ca^{2+} concentrations: the A-site and the I-site. The A-site is a high affinity Ca^{2+} binding site that mediates RYR1 opening. The I-site is a lower affinity site that mediates the protein's closing. Caffeine, halothane, and other triggering agents act by drastically increasing the affinity of the A-site for Ca^{2+} and concomitantly decreasing the affinity of the I-site in mutant proteins. Mg^{2+} also affect RYR1 activity, causing the protein to close by acting at either the A- or I-sites. In MH mutant proteins, the affinity for Mg^{2+} at either one of these sites is greatly reduced. The end result of these alterations is greatly increased Ca^{2+} release due to a lowered activation and heightened deactivation threshold. The process of sequestering this excess Ca^{2+} consumes large amounts of adenosine triphosphate (ATP), the main cellular energy carrier, and generates the excessive heat (hyperthermia) that is the hallmark of the disease. The muscle cell is damaged by the depletion of ATP and possibly the high temperatures, and cellular constituents "leak" into the circulation, including potassium, myoglobin, creatine, phosphate and creatine kinase.

The other known causative gene for MH is *CACNA1S*, which encodes an L-type voltage-gated calcium channel α-subunit. There are two known mutations in this protein, both affecting the same residue, R1086.[9][10] This residue is located in the large intracellular loop connecting domains 3 and 4, a domain possibly involved in negatively regulating RYR1 activity. When these mutant channels are expressed in human embryonic kidney (HEK 293) cells, the resulting channels are five times more sensitive to activation by caffeine (and presumably halothane) and activate at 5–10mV more hyperpolarized. Furthermore, cells expressing these channels have an increased basal cytosolic Ca^{2+} concentration. As these channels interact with and activate RYR1, these alterations result in a

drastic increase of intracellular Ca^{2+}
, and, thereby, muscle excitability.

Other mutations causing MH have been identified, although in most cases the relevant gene remains to be identified.

Animal model

Research into malignant hyperthermia was limited until the discovery of "porcine stress syndrome" (PSS) in Danish Landrace and other pig breeds selected for muscling, a condition in which stressed pigs develop "pale, soft, exudative" flesh (a manifestation of the effects of malignant hyperthermia) rendering their meat less marketable at slaughter. This "awake triggering" was not observed in humans, and initially cast doubts on the value of the animal model, but subsequently, susceptible humans were discovered to "awake trigger" (develop malignant hyperthermia) in stressful situations. This supported the use of the pig model for research. Pig farmers use halothane cones in swine yards to expose piglets to halothane. Those that die were MH-susceptible, thus saving the farmer the expense of raising a pig whose meat he would not be able to market. This also reduced the use of breeding stock carrying the genes for PSS. The condition in swine is also due to a defect in ryanodine receptors.

Gillard *et al.* discovered the causative mutation in humans only after similar mutations had first been described in pigs.

Horses also suffer from malignant hyperthermia. A causative mutated allele, ryanodine receptor 1 gene (RyR1) at nucleotide C7360G, generating a R2454G amino acid substitution. MH has been identified in the American Quarter Horse and breeds with Quarter Horse ancestry, inherited as an autosomal dominant It can be caused by overwork, anesthesia, or stress. In dogs, its inheritance is autosomal recessive.[1]

An MH mouse has been constructed, bearing the R163C mutation prevalent in humans. These mice display symptoms similar to human MH patients, including sensitivity to halothane (increased respiration, body temperature, and death). Blockade of RYR1 by dantrolene prevents adverse reaction to halothane in these mice, as with humans. Muscle from these mice also shows increased K^{+}
-induced depolarization and an increased caffeine sensitivity.

Diagnosis

During an attack

The earliest signs are early masseter muscle contracture following administration of succinylcholine, a rise in end-tidal carbon dioxide concentration (despite increased minute ventilation), unexplained tachycardia, and muscle rigidity.[1] Despite the name, elevation of body temperature is often a late sign. Other signs may include acidosis, tachypnea (in a spontaneously breathing patient), cyanosis, hypertension, cardiac dysrhythmias and hyperkalemia. Core body temperatures should be measured in any patient undergoing general anesthesia longer than 20 minutes.

Malignant hyperthermia is diagnosed on clinical grounds, but various investigations are generally performed. This includes blood tests, which may show a raised creatine kinase level, elevated potassium, increased phosphate (leading to decreased calcium) and—if determined—raised myoglobin; this is the result of damage to muscle cells. Metabolic acidosis and respiratory acidosis (raised acidity of the blood) may both occur. Severe rhabdomyolysis may lead to acute renal failure, so kidney function is generally measured on a frequent basis.

Patients may also get cardiac arrythmias (PVCs) due to the increased levels of potassium released from the muscles during episodes.

Susceptibility testing

In those who have experienced an episode of MH, further testing is not usually useful, as even a normal test does not mean there is no risk of recurrence. The exception would be if it is unclear whether the initial attack was due to a different medical problem, such as sepsis.

Muscle testing

The main candidates for testing are those with a close relative who has suffered an episode of MH or has been shown to be susceptible. The standard procedure is the "caffeine-halothane contracture test", CHCT. A muscle biopsy is carried out at an approved research center, under local anesthesia. The fresh biopsy is bathed in solutions containing caffeine or halothane and observed for contraction; under good conditions, the sensitivity is 97% and the specificity 78%. Negative biopsies are *not* definitive, so any patient who is suspected of MH by their medical history or that of blood relatives is generally treated with nontriggering anesthetics, even if the biopsy was negative. Some researchers advocate the use of the "calcium-induced calcium release" test in addition to the CHCT to make the test more specific.

Less invasive diagnostic techniques have been proposed. Intramuscular injection of halothane 6 vol% has been shown to result in higher than normal increases in local pCO among patients with known malignant hyperthermia susceptibility. The sensitivity was 100% and specificity was 75%. For patients at similar risk to those in this study, this leads to a positive predictive value of 80% and negative predictive value of 100%. This method may provide a suitable alternative to more invasive techniques. A 2002 study examined another possible metabolic test. In this test, intramuscular injection of caffeine was followed by local measurement of the pCO
2; those with known MH susceptibility had a significantly higher pCO
2 (63 versus 44 mmHg). The authors propose larger studies to assess the test's suitability for determining MH risk.

Genetic testing

Genetic testing is being performed in a limited fashion to determine susceptibility to MH. In people with a family history of MH, analysis for *RYR1* mutations maybe useful.

Criteria

A 1994 consensus conference led to the formulation of a set of diagnostic criteria. The higher the score (above 6), the more likely a reaction constituted MH:

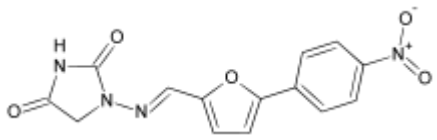
- Respiratory acidosis (end-tidal CO
  2 above 55 mmHg/7.32 kPa or arterial pCO
  2 above 60 mmHg/7.98 kPa)
- Heart involvement (unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation)
- Metabolic acidosis (base excess lower than -8, pH <7.25)
- Muscle rigidity (generalized rigidity including severe masseter muscle rigidity)
- Muscle breakdown (CK >20,000/L units, cola colored urine or excess myoglobin in urine or serum, potassium above 6 mmol/l)
- Temperature increase (rapidly increasing temperature, T >38.8°C)
- Other (rapid reversal of MH signs with dantrolene, elevated resting serum CK levels)
- Family history (autosomal dominant pattern)

Prevention

In the past, the prophylactic use of dantrolene was recommended for MH susceptible patients undergoing general anesthesia. However, multiple retrospective studies have demonstrated the safety of trigger-free general anesthesia in these patients in the absence of prophylactic dantrolene administration. The largest of these studies looked at the charts of 2214 patients who underwent general or regional anesthesia for an elective muscle biopsy. About half (1082) of the patients were muscle biopsy positive for MH. Only five of these patients exhibited symptoms consistent with MH, four of which were treated successfully with parenteral dantrolene, and the remaining one recovered with only symptomatic therapy. After weighing its questionable benefits against its possible adverse effects (including nausea, vomiting, muscle weakness and prolonged duration of action of nondepolarising neuromuscular blocking agents), experts no longer recommend the use of prophylactic dantrolene prior to trigger-free general anesthesia in MH susceptible patients.

Anaesthesia for known MH susceptible patients requires avoidance of triggering agents (all volatile anaesthetic agents and succinylcholine). All other drugs are safe (including nitrous oxide), as are regional anaesthetic techniques. Where general anaesthesia is planned, it can be provided safely by removing vaporisers from the anaesthetic machine, placing a new breathing circuit on the machine, flushing the machine and ventilator with 100% oxygen at maximal gas flows for 20–30 minutes, and inducing and maintaining anaesthesia with nontriggering agents (e.g.: propofol). Modern anaesthetic machines have more rubber and plastic components which provide a reservoir for volatile anaesthetics, and should be flushed for 60 minutes.

Treatment



Dantrolene sodium, the only available medical treatment for malignant hyperthermia

The current treatment of choice is the intravenous administration of dantrolene, the only known antidote, discontinuation of triggering agents, and supportive therapy directed at correcting hyperthermia, acidosis, and organ dysfunction. Treatment must be instituted rapidly on clinical suspicion of the onset of malignant hyperthermia.

Dantrolene is a muscle relaxant that appears to work directly on the ryanodine receptor to prevent the release of calcium. After the widespread introduction of treatment with dantrolene, the mortality of malignant hyperthermia fell from 80% in the 1960s to less than 10%. Dantrolene remains the only drug known to be effective in the treatment of MH.

Its clinical use has been limited by its low water solubility, leading to requirements of large fluid volumes, which may complicate clinical management. Azumolene is a 30-fold more water-soluble analogue of dantrolene that also works to decrease the release of intracellular calcium by its action on the ryanodine receptor. In MH susceptible swine, azumolene was as potent as dantrolene. It has yet to be studied *in vivo* in humans, but may present a suitable alternative to dantrolene in the treatment of MH.

Research in mouse models suggests that azumolene "is likely uncoupling the efficiency of a Ca^{2+}
-dependent RyR1 signal coupled directly or indirectly to the [store-operated calcium entry] machinery." There may be two different pathways of store-operated calcium entry: one, RyR1-

reliant and the other, RyR1-non-reliant (see Disease Mechanism section above for RyR1 description). Furthermore, elucidating earlier ideas on the pathogenesis of malignant hyperthermia, researchers point out that it may be "as much a syndrome of exaggerated Ca2+ entry as it is of exaggerated Ca2+
release."

Azumolene has also been shown to be as effective as dantrolene at preventing and reversing contracture in in vitro experiments with human skeletal muscle.

Prognosis

Prognosis is poor if this condition is not aggressively treated. In the 1970s, mortality was greater than 80%; with the current management, however, mortality is now less than 5%.

Epidemiology

The incidence is between 1:5,000 to 1:50,000–100,000 procedures involving general anaesthesia. This disorder occurs worldwide and affects all racial groups. Most cases, however, occur in children and young adults, which might be related to the fact many older people will have already had surgeries and thus would know about and be able to avoid this condition.

History

The syndrome was first recognized in Royal Melbourne Hospital, Australia in an affected family by Denborough *et al.* in 1962. Denborough did much of his subsequent work on the condition at the Royal Canberra Hospital. Similar reactions were found in pigs. The efficacy of dantrolene as a treatment was discovered by South African anesthesiologist Gaisford Harrison and reported in a 1975 article published in the *British Journal of Anaesthesia*.[33] After further animal studies corroborated the possible benefit from dantrolene, a 1982 study confirmed its usefulness in humans.[