MALIGNANT HYPERTHERMIA

Surgical Specialty:	All
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Background:

- General Considerations
  - Malignant hyperthermia (MH) is an inherited, pharmacogenetic disorder of the skeletal muscle when exposed to halogenated volatile anesthetics and the depolarizing muscle relaxant succinylcholine.
  - It occurs as a result of the uncontrolled release of calcium from the sarcoplasmic reticulum of skeletal muscle cells. This results in a hypermetabolic state, leading to increased carbon dioxide production, increased core temperature, and generalized muscle rigidity with resultant rhabdomyolysis, acidosis, and hyperkalemia.[1] Mortality has markedly dropped from 70% to 10% due to better identification of susceptible individuals, the routine use of capnography, a better understanding of the pathogenesis, and the widespread availability of dantrolene.
  - The clinical incidence varies from 1:40,000-1:250,000 but may be as high as 1:15,000 in children.[1]
- Genetics
  - The inheritance pattern of MH is autosomal dominant, which means that children, parents, and siblings of an MH-susceptible (MHS) patient have a 50% chance of inheriting MH susceptibility.
  - Ryanodine receptor gene (RYR1) mutations are responsible for 50-70% of the MHS patients while genetic mutations in CACNA1S (encoding the alpha-1S subunit of the voltage-gated calcium channel) and STAC3 (encoding Stac3 protein) account for ~ 1% cases of MH susceptible patients. A homozygous STAC3 mutation has been linked to Native American myopathy. There are more than 400 mutations associated with RYR1 gene, but only 34 of them are linked to MH.[2]
  - Most MHS mutations display incomplete penetrance meaning that MH will manifest in less than 100% of genetically susceptible individuals who are exposed to a triggering agent. There is also variability in the clinical expression of the syndrome among individuals, and between anesthetic episodes in the same individual when exposed to a triggering agent. The MHS patient may undergo several uneventful anesthetics (on an average three) before developing MH. Genetic complexity may be responsible for this variation in the severity and clinical presentation.[3,4]
- Diagnostic testing in patients with MHS
  - The two diagnostic options for individuals suspected to be at high risk of MH include muscle contracture testing (called the Caffeine-Halothane Contracture Test, CHCT in North America and In-Vitro Contracture Test, IVCT in Europe), and genetic testing (ryanodine receptor gene sequencing).

    - Muscle contracture testing is considered the gold standard as it is highly sensitive, and negative results rule out a diagnosis of MHS. But it has a 20% false positive rate, and patients with a positive contracture test should undergo genetic testing for a causative genetic mutation.
    - Genetic testing is considered an advanced alternative to the muscle contracture test. Once a causative mutation is found, family members can be tested for that specific causative mutation; if found, the individual can be safely labeled as MHS, and a muscle biopsy for contracture testing can be avoided.
    - However, not all mutations that cause MH have been identified, so genetic testing has a very high false-negative rate but despite that, most patients undergo genetic testing first instead of a CHCT/IVCT as the latter is both invasive and costly. Patients with negative genetic results should be offered contracture testing to confirm their MH-negative status. Some patients choose not to get tested, thus labeling themselves and their blood relatives as MHS, which changes future anesthetic plans, employment opportunities, and health insurance plans.[5,6]
- Related disorders:
    - Myopathies associated with ryanodine receptor abnormalities are MHS and include King-Denborough syndrome (KDS), central core disease (CCD), and multi-minicore myopathy.
    - Non-anesthesia-related MH or awake MH-patients with a history of unexpected rhabdomyolysis triggered by either heat or exercise may be more prone to MH and vice versa due to a similar genetic mutation. While the trigger of exertional heat illness (EHI) is different than that of MH, the end result of excessive body temperature is very similar. Some experts advocate treating these patients as MHS and suggest genetic testing for an MH-causative mutation. [7]

Anesthetic Planning:

- Pre-Anesthetic Evaluation
    - If the patient or a blood relative has a history of MH or is suspected of being MHS, they should receive a non-triggering anesthetic. Lack of MH events in a more immediate relative or the patient itself with past anesthetics is not reassuring as MHS patients may have many uneventful anesthetics before developing the full-blown episode.[6]
    - History of any congenital myopathy or muscular dystrophy in the blood relatives should be ruled out as patients with some congenital myopathies are associated with MH, and patients with undiagnosed muscle dystrophy, although not MH susceptible can develop anesthesia-induced rhabdomyolysis (AIR) when exposed to triggering agents. [7] If an increased risk of developing MH under anesthesia cannot be excluded, then the patient should be treated as MHS.
- Specific Room Set-Up Requirements
    - Remove succinylcholine and vaporizers from the anesthesia machine to prevent their inadvertent use. Prepare the anesthesia machine by flushing off any residual halogenated volatile gases via either the standard method of flushing or by using activated charcoal filters (ACF). The accepted safe concentration of inspired volatile anesthetic is 5 ppm or less for an MHS patient. [8]
- Anesthesia machine preparation using the standard flushing method
    - Remove vaporizers, attach a new breathing circuit and soda lime canister, and then flush the circuit by continuously using maximum fresh-gas flow (FGF) rates for the workstation-specific time. The ventilator should also be included in purging the machine by cycling the ventilator at the time of the oxygen flow.

  - Modern and more complex anesthetic workstations seem to require a prolonged time to wash out volatile agents because of their complex internal plastic parts that capture and release volatile anesthetic molecules. The time widely differs from 10 to 104 minutes. [9] Once the machine has been prepared, FGF of 10 L/min should be maintained throughout the case to avoid volatile anesthesia concentration rebound.
- Anesthesia machine preparation using Activated charcoal filters (ACF).
  - Activated charcoal captures and holds volatile anesthetic molecules on its porous surface. They do not clean the complete workstation, rather adsorb residual volatile anesthetic in the breathing circuit. Vapor-Clean is the only FDA-approved ACF device for filtering anesthetic gases in MH cases. Filters effectively reduce volatile anesthetic concentrations to <5 ppm within <1.5 minutes after inserting just one ACF and flushing the breathing circuit for 90 seconds with 10 L/min FGF even without changing uncontaminated equipment. Once the machine has been prepared, the FGF can be reduced to 3 L/ min but not less than 1 L/min. ACFs should be changed after 12 hours. [8,9]

Intraoperative Considerations:

- Signs/ symptoms of MH
  - Common signs include increased end-tidal carbon dioxide ($ETCO_2$), tachycardia, cardiac arrhythmias, rigidity, mixed respiratory and metabolic acidosis, hyperkalemia, and myoglobinuria, with the most frequent initial signs being hypercarbia, tachycardia, and hyperthermia.
  - The early signs can be mistaken for inadequate anesthesia or febrile reaction but a brief trial of deeper anesthesia failing to slow the heart rate or vigorous mechanical ventilation failing to reduce the $ETCO_2$ or a very rapid rate of temperature increase (as high as 1-2 degree Celsius every five minutes) should raise the suspicion of possible MH reaction. Blood gas will show unexplained acidosis and hyperkalemia.
  - Muscle rigidity may be an early sign but is not always present. It does not respond to non-depolarizing neuromuscular blockers. It may be limited to masseter spasm, observed after administration of succinylcholine. [1,10]
  - MH can occur at any time during anesthesia or rarely in the early postoperative period. As per North American Malignant Hyperthermia Registry, postoperative MH is uncommon and is generally seen within less than an hour of discontinuation of volatile agents. If postoperative MH occurs beyond this time interval, it should warrant investigation of an alternative diagnosis. Rhabdomyolysis is reported to be a more common presentation of postoperative MH rather than classic MH episode. [11]
- Differential diagnosis
  - Hypercarbia can result from hypoventilation or laparoscopic surgery; hyperthermia can occur from iatrogenic overheating or sepsis. Other hypermetabolic conditions that can mimic MH include thyrotoxicosis, pheochromocytoma, neuroleptic malignant syndrome, serotonin syndrome, and intoxication with drugs such as cocaine. [1,2]
- Management
  - At the first suspicion of MH reaction, discontinue triggering agents immediately, and hyperventilate with 100% oxygen at high gas flows. Simultaneously call for help and resuscitation drugs (MH Cart). If available, place charcoal filters on the inspiratory and expiratory limbs of the anesthesia circuit to reduce volatile agent concentration to minimum levels. Administer dantrolene promptly (see dosage below).
  - Insert an arterial line for blood pressure monitoring and blood sampling for blood gases, potassium, lactate, creatine kinase (CK), and myoglobin levels. Treat severe metabolic acidosis with sodium bicarbonate, hyperkalemia with glucose insulin

infusions, and life-threatening hyperkalemia with calcium chloride. Avoid calcium channel blockers with dantrolene as they can interact to produce fatal hyperkalemia. Monitor urine output with a foley catheter and maintain hydration to prevent acute renal failure. Use external and internal cooling to a target core temperature of no more than 38.5 degrees Celsius.
    - Continue resuscitation in the intensive care unit (ICU) and follow serial concentrations of CK, liver enzymes, coagulation profile, and renal function.[5,6]
- Dantrolene
    - It acts by decreasing calcium release from the sarcoplasmic reticulum leading to skeletal muscle relaxation. Revento (generic) and Ryanodex are the two preparations of dantrolene. Generic is a lyophilized powder with 20 mg dantrolene and 3 g mannitol and requires 60 cc of sterile water for reconstitution. Ryanodex is the newer formulation with 250 mg of dantrolene and 125 mg of mannitol and requires only 5 ml of sterile water for reconstitution.[1] The initial dose of dantrolene is 2.5 mg/kg IV bolus rapidly followed by additional doses of 1 mg/kg as frequently as needed (no minimum time between doses) until the patient responds with a decrease in $ETCO_2$, decreased muscle rigidity, and/or lowered heart rate. All physiologic parameters should rapidly normalize over 45 minutes, and most acute MH reactions are completely controlled with 10mg/kg of IV dantrolene (4 doses of 2.5 mg/kg). One should consider an alternative diagnosis if this dose is reached without symptomatic improvement. It should be administered rapidly via a large vein to avoid thrombophlebitis or thrombosis. Prophylaxis is not recommended in MHS patients.[5,6]
- Post-op Care
    - Patients who have had a MH reaction should be closely monitored in the ICU. They should continue to receive dantrolene 1 mg/kg every 4-6 hours for at least 24 hours or longer if indicated to prevent recrudescence (recurrence of MH signs after successful initial treatment of the acute event) that may occur in 25% of cases.[12] Continue to monitor arterial blood gases, serum CK, potassium and calcium, urine and serum myoglobin, and clotting factors every six hours until they return to normal values.
    - After the acute episode is over, the patient and family should be counseled regarding MH and the possibility of MH susceptibility in other family members. The patient should be advised to undergo molecular genetic testing, and if a causal mutation is found, then this can be used to confirm MHS in other family members. These patients should also be informed that they might be at a higher-than-normal risk of exertional heat illness.[5,6]
    - Patients with known MHS who have had an uneventful, trigger- free anesthetic can be discharged the same day. A minimum of an hour in the postanesthesia care unit (PACU) and an additional hour in phase 2 PACU or step down unit is recommended (policy may vary from institution to institution).[5]

Case Specific Complications/Pitfalls

- Patients with Duchenne's and Becker's muscular dystrophy are not MHS, although they can also develop rhabdomyolysis and life-threatening hyperkalemia when exposed to the same triggering agents. This phenomenon is termed AIR, but unlike MH, no hypermetabolism is seen in AIR. The risk of AIR is highest in Duchene's and Becker's muscular dystrophies, and low in the rest of the muscular dystrophies.
- Patients with mitochondrial myopathy are not MHS as was previously thought.[7]
- One should avoid succinylcholine in patients with myotonic dystrophy as it can result in a myotonic reaction or exaggerated contractures, which can make intubation difficult or

impossible. Myotonia is the result of a change in the muscle itself, not the neuromuscular junction, so pharmacologic paralysis will have no effect on a myotonic reaction.

- Infants with undiagnosed hypotonia coming for surgery present unique anesthetic challenges. The unknown diagnoses of hypotonia (after ruling out common causes) from muscular dystrophies vs. central core disease vs. mitochondrial disorder have conflicting anesthetic management implications. The safest anesthesia approach would be "non-triggering, non-propofol" based technique.[12]

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