Malignant Hyperthermia

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- Malignant hyperthermia (MH) is a pharmacogenetics disorder that manifests as a hypermetabolic response to potent inhalation agents
    - Halothane, isoflurane, sevoflurane, desflurane
    - Also can occur with succinylcholine
    - Stressors such as exercise and heat may also induce MH
- MH is a genetic disorder: Causative mutations in the RYR1 and CACNA1S genes

Etiology

- The incidence of MH episodes during anesthesia is between 1:10,000 and 1:250,000 anesthetics.
- Patients require three anesthetics before triggering, on average
- Reactions develop more frequently in males than females (2:1)

Clinical Manifestation

- MH may occur at any time during anesthesia as well as in the early postoperative period, but not after an hour of discontinuation of volatile agents
- The key clinical features include:
    1. An unexplained elevation of expired carbon dioxide, despite increased minute ventilation
    2. Muscle rigidity
    3. Rhabdomyolysis
    4. Hyperthermia
    5. Tachycardia
    6. Acidosis
    7. Hyperkalemia
- The uncontrolled hypermetabolic response leads to respiratory and metabolic acidosis due to rapid consumption of energy stores and ATP
- If untreated, rapid myocyte death and rhabdomyolysis occurs, resulting in life – threatening hyperkalemia
- Myoglobinuria may lead to renal failure
- Disseminated intravascular coagulation (DIC) is the usual cause of death if body temperatures exceed 41 degrees
- **Rhabdomyolysis**: the breakdown of skeletal muscle, which is associated with excretion of myoglobin in the urine.

Pharmacological Triggers

- All inhalation anesthetics except nitrous oxide, as well as the muscle relaxant succinylcholine are triggers for MH.

- No other anesthetic drugs appear to be triggers, including propofol and ketamine. Neither are catecholamines, nondepolarizing muscle relaxants, catechol congeners, digitalis or similar agents

Pathophysiology

- Experimental evidence clearly indicates that the signs and symptoms of MH are related to an uncontrolled release of intracellular Ca2+ from skeletal muscle sarcoplasmic reticulum (SR)
- The enhanced intracellular Ca2+ results in abnormal skeletal muscle metabolism manifesting as activation of muscle contraction, increased oxygen consumption and CO2 production, ATP hydrolysis and heat production.
- The normal sequestration of released Ca2+ is inadequate and energy is expended in a futile manner, to lower intracellular Ca2+. The declining levels of ATP lead to failure of membrane integrity and release of potassium and Creatnine Kinase (CK)
- A defective or disordered Ca2+ channel located in the SR membrane underlies MH susceptibility. This channel is termed the ryanodine receptor (RyR1).

Diagnostic Methods

- The principal diagnostic features of MH are unexplained elevation of ETCO2 concentration, muscle rigidity, tachycardia, acidosis, hyperthermia, and hyperkalemia.
- The “gold standard” for diagnosis of MH is currently an in vitro contracture test, which is based on contracture of muscle fibers in the presence of halothane or caffeine.

Differential Diagnosis

- A syndrome often confused with MH is sudden hyperkalemic cardiac arrest during or shortly after anesthesia in young males.
- Patients with Duchenne’s muscular dystrophy are at risk to dramatic life-threatening hyperkalemia upon administration of succinylcholine.
- More recently, it has been shown that administration of potent volatile agents to such patients may produce a similar syndrome
- The patient with a dystrophinopathy that develops these anesthetic-related complications does not also exhibit classic signs of MH, such as hyperthermia or marked muscle rigidity. They may exhibit rhabdomyolysis
- Therefore, this reaction is ***not*** malignant hyperthermia, since the dystrophinopathies are caused by mutations on the X chromosome and dantrolene ***will not*** be effective.
- Disorders not associated with MH include muscular dystrophies, myotonias, neuroleptic malignant syndrome, osteogenesis imperfecta and arthrogryposis.

Management and Treatment

- Dantrolene is the only drug known to specifically treat MH.
- The essential points in the treatment of an acute MH crisis are:
    - the immediate discontinuation of trigger agents
    - hyperventilation
    - administration of dantrolene
    - cooling by all routes available (intravenous saline at 4C, topical ice to all exposed areas)
    - Hyperkalemia management: Ca2+, bicarbonate, glucose and insulin, and hyperventilation

Take Home Message

Malignant Hyperthermia remains a serious risk factor for susceptible individuals undergoing general anesthesia using volatile agents. Symptoms include an elevation of end tidal CO2, muscle rigidity, hyperthermia, tachycardia, hyperkalemia, acidosis and rhabdomyolysis. Early recognition is vital to proper treatment, which includes administration of dantrolene, discontinuation of trigger agents, cooling, and hyperkalemia management.

References

Henry Rosenberg, Neil Pollock, Anja Schiemann, Terasa Bulger and Kathryn Stowell. Malignant hyperthermia: a review. Orphanet Journal of Rare Diseases (2015) 10:93 DOI 10.1186/s13023-015-0310-1