Malignant Hyperthermia

Malignant hyperthermia is a rare, life-threatening hypermetabolic reaction in susceptible individuals triggered by volatile inhaled anesthetics and/or succinylcholine. Malignant hyperthermia susceptibility is usually inherited in an autosomal dominant pattern and is most commonly associated with pathogenic variants in RYR1, which encodes the skeletal-muscle ryanodine receptor calcium-release channel. Exposure to a triggering agent can cause uncontrolled $Ca^{2?}$ release from the sarcoplasmic reticulum, resulting in sustained muscle contraction and a hypermetabolic state. Malignant hyperthermia is treated with immediate discontinuation of triggering agents, dantrolene, and supportive care.



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Inheritance

Autosomal Dominant

Domino

Malignant hyperthermia is inherited in an autosomal dominant manner; this means that one abnormal allele is enough for the individual to manifest the disease. However, it is important to note that the penetrance of this disorder is variable; hence, not all individuals who inherit abnormal alleles will manifest the disease.

Pathophysiology and Triggers

Ryanodine Receptor 1 Mutation

Rihanna Receptor (1) Wand Mutant

Malignant hyperthermia patients have a genetic predisposition due to mutations in skeletal muscle ion channels. Ryanodine receptor 1, coded by the RYR1 gene, is a commonly affected calcium channel that controls calcium release from the sarcoplasmic reticulum. Mutations in this channel result in excessive calcium accumulation within muscle cells after exposure to potent volatile halogenated anesthetics anesthetics or succinylcholine.

Inhaled Anesthetics

A-Nest of Inhaled Anesthesia

Common triggers for malignant hyperthermia are potent volatile halogenated anesthetics given during surgery, such as halothane, isoflurane, sevoflurane, desflurane, and enflurane. Therefore, malignant hyperthermia should be suspected during anesthesia or shortly after exposure to a triggering agent when a patient develops clinical findings, such as unexplained rising end-tidal CO2, tachycardia, muscle rigidity, acidosis, hyperkalemia, or hyperthermia.

Succinylcholine

Sucker-in-cola

Succinylcholine is a depolarizing neuromuscular blocking agent often used during procedures to paralyze muscles and facilitate intubation. However, in myocytes with mutated calcium channels, succinylcholine will trigger excess calcium release and lead to malignant hyperthermia.

Increased Calcium Release From Sarcoplasmic Reticulum

Up-arrow Calcium-cow from Shark Rectangle

In malignant hyperthermia-susceptible individuals, genetic abnormalities affecting skeletal muscle calcium regulation cause Increased Calcium Release from the Sarcoplasmic Reticulum after exposure to a triggering agent. The excess intracellular calcium causes sustained skeletal muscle contraction and dramatically increases muscle metabolism. This hypermetabolic state leads to the characteristic clinical manifestations of malignant hyperthermia.

Symptoms

Hypercapnia

Hiker-cape

Hypercapnia is one of the earliest signs of malignant hyperthermia and results from excessive carbon dioxide production by hypermetabolic skeletal muscle. Despite adequate ventilation, end-tidal CO? and arterial CO? levels continue to rise. Progressive hypercapnia contributes to respiratory acidosis and helps

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distinguish malignant hyperthermia during anesthesia.

Tachycardia
Tac-heart-card
Tachycardia is an early manifestation of malignant hyperthermia caused by increased metabolic demand, rising carbon dioxide levels, and sympathetic activation. As the hypermetabolic state worsens, the heart works harder to meet the body's increased oxygen requirements. Persistent tachycardia may precede more severe cardiovascular complications.

Arrhythmia
Broken Arrhythmia-drum
Arrhythmias can develop during malignant hyperthermia as metabolic disturbances become more severe. Hyperkalemia from rhabdomyolysis, acidosis, and physiologic stress increase the risk of abnormal cardiac rhythms. Prompt treatment is essential to prevent progression to life-threatening dysrhythmias.

Muscle Rigidity
Muscle-man of Stone
Due to the overwhelming release of calcium from the sarcoplasmic reticulum, these patients remain in a state of muscle contraction that leads to muscle rigidity. A characteristic finding of muscle rigidity due to malignant hyperthermia is masseter muscle rigidity. Without treatment, sustained muscle rigidity can lead to skeletal muscle breakdown and progress to rhabdomyolysis.

Rhabdomyolysis
Rabbit-muscle-lights
Rhabdomyolysis occurs when sustained skeletal muscle contraction causes muscle fiber breakdown during malignant hyperthermia. Damaged muscle releases myoglobin, creatine kinase, and potassium into the bloodstream. These changes increase the risk of acute kidney injury and hyperkalemia.

Hyperthermia
Hiker-thermometer
Hyperthermia develops as sustained muscle contraction generates excessive heat during the hypermetabolic state of malignant hyperthermia. Although it gives the disorder its name, elevated body temperature is often a later finding rather than the earliest sign. Rapid recognition before severe hyperthermia develops improves patient outcomes.

Acidosis
Acidic-lemon
Acidosis develops because hypermetabolic skeletal muscle produces excessive carbon dioxide and consumes large amounts of ATP. This results in both respiratory acidosis from hypercapnia and metabolic acidosis from increased lactate production. Signs may include elevated PaCO?, increased lactate, and decreased blood pH. Worsening acidosis contributes to cardiovascular instability and increases the risk of arrhythmias.

Treatment

Treat Underlying Cause
Treating Underlying Attacker
Treatment of malignant hyperthermia begins with immediately discontinuing the triggering anesthetic or succinylcholine and administering dantrolene, which inhibits further calcium release from the sarcoplasmic reticulum. Supportive care includes active cooling, correction of acidosis and electrolyte abnormalities, and treatment of complications such as rhabdomyolysis and arrhythmias. Early intervention is lifesaving and significantly reduces mortality.

Dantrolene
Denture-lion
Dantrolene is the treatment for malignant hyperthermia. It directly inhibits the ryanodine receptor in myocytes, thereby preventing calcium release from the sarcoplasmic reticulum of muscle cells.

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