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Malignant Hyperthermia for the Nurse Anesthetist

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Malignant Hyperthermia

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Topic Introduction

- Malignant Hyperthermia (MH) is a rare autosomal dominant genetic disorder that is triggered in the presence of halogenated inhalational anesthetic gasses and the depolarizing neuromuscular blocking agent succinylcholine.
- The first identified case of MH was in the 1960's when a patient with a family history of anesthesia complications demonstrated hyperthermia, rapid heart rate, and hypotension after induction of anesthesia (Seifert et al., 2015).
- Failure of early recognition of MH can lead to multisystem organ failure, permanent neurological damage, disseminated intravascular coagulopathy (DIC), cardiac failure, and death if left untreated (Seifert et al., 2015).
- A coordinated care effort is essential to recognize and treat an MH crisis and all operating room personnel are required to undergo MH crisis training (MHAUS, 2020).

Topic Relevance and Importance

- MH can present in patients who have previously received anesthesia with triggering agents with no reactions in the past (Nagelhout & Plaus, 2018, p 775).
- Presentation of signs and symptoms of MH can be of varying magnitude and severity and mimic other pathologic processes including neuroleptic malignant syndrome, thyroid storm, sepsis, and pheochromocytoma (Gupta & Hopkins, 2017). This makes definitive diagnosis of MH difficult which can lead to a delay in treatment and poor clinical outcomes.
- Signs and symptoms can present immediately after exposure to triggering agents up until approximately one hour after discontinuation of triggering anesthetics (Rosenberg et al., 2015).
- It is the responsibility of the anesthesia provider to recognize the occurrence of MH, direct treatment, and coordinate care with other providers to ensure optimal clinical outcomes for patients exhibiting this rare but life-threatening disorder.
- MH can only be triggered by certain anesthetic agents. Proper preparation and avoidance of these triggering agents renders the likelihood of an MH crisis occurring impossible and ensures patient safety. This illustrates the importance of adequate preoperative assessment including family history of unexplained death during anesthesia. The anesthetist must have adequate knowledge of the pathophysiologic process of MH and take appropriate steps necessary to ensure it does not occur.

Incidence & Epidemiology

- Incidence of 1:10,000 to 1:250,000 anesthetics; prevalence of genetic abnormalities may be as high as 1:400 (Rosenberg et al., 2015).
- On average, patients require three anesthetics before a crisis is triggered (Rosenberg et al., 2015).
- All ethnic groups affected in all parts of the world (Rosenberg et al., 2015).
- MH reactions are more common in males (62%) than females (38%) (Gupta & Hopkins, 2017).
- Highest incidence of disease presentation in young adults, with a "mean age of all patients experiencing reactions of 18.3 years old" (Rosenberg et al., 2015).

Genetic Predisposition and Susceptible Populations

- 3 genetic alterations associated with MH susceptibility: *CACNA1S*, *STAC3*, and *RYR1* genes (Litman et al., 2018).
- Autosomal Dominance: 50% of offspring of affected individuals inherit genetic defect.
- All family members of a patient with known MH susceptibility must also be considered MH susceptible until proven otherwise (MHAUS, 2020).
- Patients with certain myopathies have genetic defects associated with MH and must be considered susceptible to MH by the anesthetist (Litman et al., 2018):
  - Central Core Disease
  - Duchenne Muscular Dystrophy
  - Congenital Fiber Disproportion
  - Multiminicore Myopathy
  - Native America Myopathy
  - Becker Muscular Dystrophy
  - King-Denborough Syndrome
  - Periodic Paralysis
  - Centronuclear Myopathy

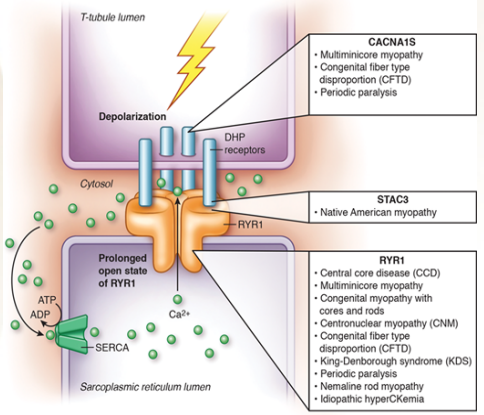

Figure 1. Myopathies Associated with MH (Litman et al., 2018).

Underlying Pathophysiology

Normal Skeletal Muscle Physiology

- Action potential from motor neuron travels to presynaptic terminal.
- Acetylcholine is released into the synaptic cleft and binds with the postsynaptic skeletal muscle nicotinic membrane receptor, which then depolarizes adjacent muscle fibers.
- Calcium (Ca^{2+}) channels open, Ca^{2+} rushes into cell, and additional Ca^{2+} is released from the sarcoplasmic reticulum (SR) via the ryanodine receptors (Hernandez-Ochoa & Schneider, 2018).
- Normal skeletal muscle contains ryanodine receptors which regulate Ca^{2+} movement from the SR to the cytoplasm of the muscle cell (Litman et al., 2018).
- Ca^{2+} binds to troponin enabling cross-bridging of actin & myosin, causing muscle contraction using adenosine triphosphate (ATP) to create *work* and *heat* (Gupta & Hopkins, 2017).
- Ca^{2+} is then removed from the cytoplasm of the cell back into the SR via the SERCA channel to enable muscle fiber relaxation (Gupta & Hopkins, 2017). This process is collectively known as excitation-contraction coupling (ECC).

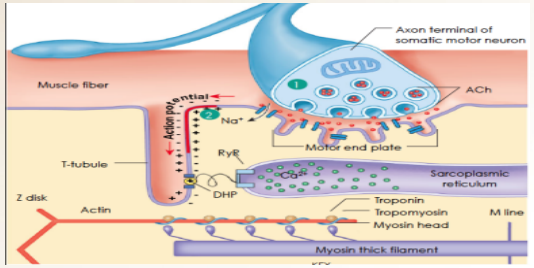

Figure 2. Normal Skeletal Muscle Physiology (Hernandez-Ochoa & Schneider, 2018).

Skeletal Muscle Pathophysiology in Malignant Hyperthermia

- MH-susceptible patients demonstrate a defective ryanodine receptor (RYR1) related to the SR in skeletal muscle cells (Rosenberg et al., 2015).
- The defective RYR1 receptor results in unopposed release of SR Ca++ stores into the cytoplasm in the presence of triggering anesthetic agents (Litman et al., 2018).
- The SERCA channel of the SR Ca^{2+} sequestering mechanism becomes overwhelmed, causing Ca^{2+} to build up in the skeletal muscle cell cytoplasm leading to sustained muscle contraction (Litman et al., 2018).
- Sustained contraction causes increased energy use, dramatic rises in CO_2 production, increased O_2 consumption, and production of heat and lactic acid (Gupta & Hopkins, 2017).

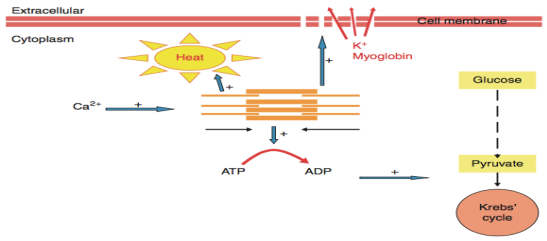

Figure 3. Pathologic Process of Defective RYR1 Receptor (Gupta & Hopkins, 2017).

Significance of Pathophysiology

- Dysregulation of Ca^{2+} in skeletal muscle causes hypermetabolic state and high demand for ATP (Gupta & Hopkins, 2017).
- Increased CO_2 production and O_2 consumption leads to a mixed acidosis (Gupta & Hopkins, 2017).
- Sustained muscle contraction compromises cell membrane integrity causing hyperkalemia, myoglobinemia, rhabdomyolysis, and acute kidney injury (Gupta & Hopkins, 2017).
- Hyperthermia from high metabolic state predisposes patient to DIC and bleeding in the presence of invasive surgical procedures.
- Hypercapnia, hyperkalemia, and tachycardia predispose the patient to cardiac arrhythmias, cardiovascular collapse, and death.

Signs and Symptoms

Early Signs & Symptoms (Gupta & Hopkins, 2017)

- Sudden, unexplained rise in end-tidal carbon dioxide ($EtCO_2$).
- Rapid heart rate (tachycardia).
- Tachypnea in the spontaneously breathing patient.
- Diaphoresis.
- Masseter muscle or generalized muscle rigidity.
- Unexplained fever in the immediate postoperative period.

Late Signs & Symptoms (Gupta & Hopkins, 2017)

- Hyperthermia caused by sustained muscle contraction.
- Lactic acidosis.
- Hyperkalemia, peaked T-waves.
- Myoglobinemia from muscle breakdown (similar to rhabdomyolysis).
- Dark colored urine.
- Hypotension.
- Cardiac arrhythmias.
- Coagulopathies and disseminated intravascular coagulopathy.
- Cardiovascular collapse and death.

Diagnosis

- Based on clinical presentation: unexplained $EtCO_2$, muscle rigidity, tachycardia, acidosis, hyperthermia, and hyperkalemia (Rosenberg et al., 2015).
- **Gold Standard:** caffeine/halothane contraction test (CHCT)- muscle biopsy from thigh is exposed to caffeine and/or halothane. A positive result consists of sustained visible contraction upon exposure to triggering agents (Gupta & Hopkins, 2017).
- CHCT is painful, expensive, and only performed at a small amount of specialized testing centers (Rosenberg et al., 2015).

Implications for Nurse Anesthetists

Prevention: the goal of anesthetic management of MH-susceptible patients is prevention of a crisis, including ensuring the anesthesia machine has been properly prepared by flushing with high-flow O_2 for brand-specific timeframe, charcoal filters applied to inspiratory and expiratory limbs of circuit if available, anesthesia gas vaporizers have been removed from the machine, and administering no triggering agents (MHAUS, 2020).

MH-Triggering Agents:

- Succinylcholine
- Desflurane
- Isoflurane
- Sevoflurane
- Halothane

Management of an MH Crisis:

**It is the responsibility of the anesthetist to recognize and treat an MH crisis.*

- Stop administration of triggering agents.
- Alert surgeon of the need to stop procedure.
- Hyperventilate with 100% FiO2, attach charcoal filters to breathing circuit if available, and change breathing circuit and gas absorbent canister.
- Call for assistance from other anesthesia providers.
- Give Dantrolene 2.5mg/kg initial dose, 1mg/kg as needed for persistent signs of MH.
- Cool patient to core temperature <38.5°C via cooling blankets, cold IV fluid, and cold gastric/ bladder lavages as necessary.
- Insert arterial and large-bore IV/ central line for blood pressure monitoring, frequent lab draws, and IV fluid administration.
- IV fluids to prevent kidney injury and cardiovascular collapse.
- Treat electrolyte & pH abnormalities.
- Treat cardiac arrhythmias as needed.
- Treat coagulopathies as needed.
- Ensure patient is monitored in critical care unit for a minimum of 24 hours after MH signs and symptoms are controlled.

**All management information from Gupta & Hopkins, 2017.*

Dantrolene Sodium: the only know treatment for MH works by "depressing the ECC in skeletal muscle by binding to the RYR1 receptor and decreasing intracellular calcium concentration" (Ratto & Joyner, 2020). Comes in two preparations:

- **Dantrium™** IV (20mg dantrolene/vial; requires 60mL sterile H2O for reconstitution).
- **Ryanodex™** IV (250mg dantrolene/vial; requires 5mL sterile water for reconstitution).

Conclusions

- Malignant Hyperthermia is a rare, autosomal dominant skeletal muscle disorder that can have an insidious onset, difficult diagnosis, and lead to morbidity and mortality in the surgical patient.
- MH crisis-triggering agents are the depolarizing neuromuscular paralytic succinylcholine and anesthetic gasses halothane, desflurane, sevoflurane, and isoflurane. MH can occur in patients who have received anesthesia with these agents in the past (Nagelhout & Plaus, 2018, p 775).
- It is the responsibility of the anesthetist to perform an adequate preoperative patient history evaluation to uncover possible MH susceptibility in the surgical patient. Patients with a family history of MH or associated skeletal muscle disorder must be treated as MH-susceptible until proven otherwise via CHCT at an approved facility.
- Failure to detect an MH crisis can lead to kidney failure, profound acidosis, coagulopathies, rhabdomyolysis, cardiac dysrhythmias, cardiovascular collapse, and death (Seifert et al., 2015).
- Early detection of an MH crisis and treatment with Dantrolene affords the patient with the greatest chance of survival in the intraoperative and postoperative period. An MH crisis requires an adequately prepared surgical team and high level of coordinated care to ensure optimal outcomes in patients exhibiting a malignant hyperthermia crisis.

References

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