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Malignant Hyperthermia

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Introduction

Malignant Hyperthermia (MH) is a rare but life-threatening, genetic condition that can manifest when a patient is exposed to certain inhalation agents used in anesthesia as well as the depolarizing muscle relaxant succinylcholine (Rosenberg, Pollock, Schiemann, Bulger, & Stowell, 2015, p. 1).

MH is an autosomal dominant trait with incomplete penetrance that has been found in "approximately 1:40,000 adults" (Creech & Zhang, 2019, p. 1). The *RYR1* gene, which encodes for calcium release channels in the sarcoplasmic reticulum, is the most prevalent gene mutation found in MH patients (Miller et al., 2018, p. 945).

Importance

MH can develop during or after a surgical procedure and if left untreated, can cause major organ system damage and death (Seifert, Wahr, Pace, Cochrane, & Bagnola, 2014, p. 189). Creating awareness of this rare genetic condition allows for quicker interventions in reversing MH.

Due to the increased awareness, genetic testing, and MH protocol, the incidence of death due to MH "has decreased in the last thirty years" (Rosenberg et al., 2015, p. 13). More specifically, MH mortality has been reduced from "80% to 1.4%" (Rosenberg et al., 2015, p. 13). The continued awareness and research of MH should be maintained to effectively decrease the mortality rates of MH.

Case Report

(Mullins, 2018)

J.M., a 24-year-old female, presented for an elective bilateral breast reduction surgery. The preoperative evaluation reported no abnormalities, but J.M. was adopted so there was no known family medical history. Anesthesia induction was performed, and vital signs remained stable. J.M. was mechanically ventilated and maintained with desflurane, fentanyl, and vecuronium.

Twenty-five minutes after induction, J.M. started to exhibit masseter spasm and the surgeon noted muscle rigidity. Simultaneously, J.M. became tachycardiac, hypertensive, dark color urine was noted, and her end-tidal carbon dioxide (EtCO2) rose to 58 mmHg. Her forehead temperature probe remained constant at 36.9 °C. The anesthesia provider suspected the onset of MH and called for additional staff members.

Epidemiology

- Incidence of MH episodes (Creech & Zhang, 2019, p. 1):
  - 1:40,000 in adults
  - 1:15,000 in pediatrics
- On average, patients require exposure to three anesthetic events before a triggering event (Rosenberg et al., 2015, p. 2).
- All ethnic groups are affected (Rosenberg et al., 2015, p. 2).
- Reactions develop more frequently in males than in females (Rosenberg et al., 2015, p. 2).
- The average age of occurrence is 18.3 years (Rosenberg et al., 2015, p. 2).
- Three genes have been associated with MH susceptibility (Miller et al., 2018, p. 945):
  - *RYR1* gene
  - *CACNA1S* gene
  - *STAC3* gene
- MH genes are inherited by an autosomal dominant pattern with incomplete penetrance (Creech & Zhang, 2019, p. 1).

Signs and Symptoms

Early Symptoms	Late Symptoms
Tachycardia	Hyperthermia
Gradual rise in EtCO2, despite increase ventilation	Disseminated intravascular coagulation (DIC)
Muscle rigidity	Rhabdomyolysis
Masseter spasm	Cardiac dysrhythmias
Tachypnea	Hyperkalemia
Sweating	Cardiac arrest

Figure 1. Signs and symptoms of MH (Rosenberg et al., 2015, pp. 2-3)

- MH may occur anytime during anesthesia administration or within one hour of discontinuation of volatile agents (Rosenberg et al., 2015, p. 2).
- Some people may only exhibit a few symptoms, making MH difficult to diagnose (Mullins, 2018, p. 538).

Excitation-contraction Coupling Process

1. Acetylcholine binds to postsynaptic nicotinic acetylcholine receptors (nAChR) located on the sarcolemma (skeletal muscle cell membrane) (Mullins, 2018, p. 583).
2. Activation of nonselective cation channels depolarize the sarcolemma and the action potential travels down the transverse tubule (t-tubule) system (Mullins, 2018, p. 583).
3. L-type voltage-gated calcium ($Ca_v1.1$) channels located in the t-tubule undergo a conformational change due to depolarization. Cav1.1 channels signal the type 1 ryanodine receptors (RyR1) to open and release calcium (Ca^{2+}) from the sarcoplasmic reticulum (SR) (Mullins, 2018, p. 583).
4. The influx of extracellular Ca^{2+} through $Ca_v1.1$ channels and intracellular release of Ca^{2+} from the SR activate muscle contraction by Ca^{2+} binding to troponin (Mullins, 2018, p. 583).

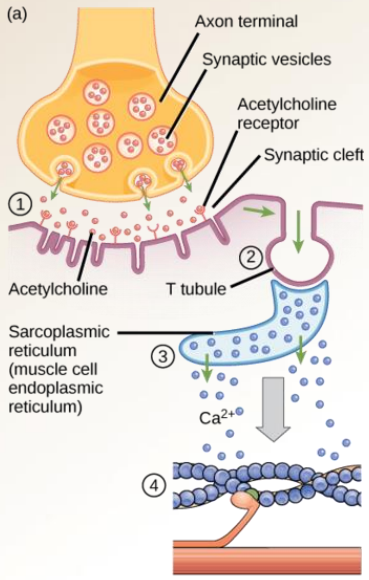

Figure 2. Excitation-contraction coupling process (Excitation-contraction coupling, 2019)

Underlying Pathophysiology

- Three genetic mutations are linked to MH susceptibility (Miller et al., 2018, p. 945):
  - *RyR1* gene: encodes the channel that releases Ca^{2+} from the SR.
  - *CACNA1S* gene: encodes the main subunit of the t-tubule voltage sensor.
  - *STAC3* gene: encodes a protein responsible for directing the voltage sensor into the correct t-tubule location and a direct role in excitation-contraction coupling.
- Signs and symptoms of MH are related to the uncontrolled release of intracellular Ca^{2+} from the SR (Rosenberg et al., 2015, p. 4).
- Increased intracellular Ca^{2+} causes abnormal skeletal muscle metabolism manifesting as (Rosenberg et al., 2015, p. 4):
  - Muscle contraction
  - Increased oxygen consumption
  - Increased carbon dioxide production
  - ATP hydrolysis
  - Heat production
- Triggering agents for MH (Seifert et al., 2014, p. 192):
  - Volatile anesthetics:
    - Desflurane
    - Enflurane
    - Isoflurane
    - Sevoflurane
  - Depolarizing neuromuscular blockers (NMB):
    - Succinylcholine
- Triggering agents' effect on Ca^{2+} release (Klingler et al., 2014, p.4):
  - Volatile anesthetics
    - Act directly on RyR1 channels to stimulate the release of Ca^{2+} from the SR.
  - Succinylcholine
    - Acts indirectly by activating the nAChR resulting in continuous cation influx.
    - Cation influx causes continuous depolarization which allows action potentials to activate the $Ca_v1.1$ channels leading to RyR1 channel activation.

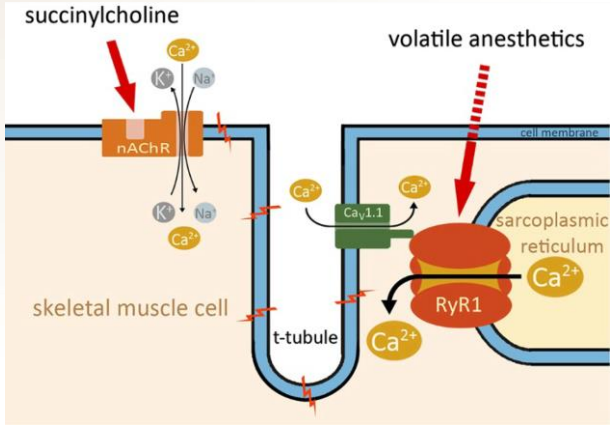

Figure 3. Triggering agents of MH mechanism of action (Klingler et al., 2014, p. 3)

Significance of Pathophysiology

- *Hypermetabolic state:* leads to respiratory and metabolic acidosis due to the rapid consumption of energy stores and ATP (Rosenberg et al., 2015, p. 2).
- *Hyperthermia*: a dramatic increase in core temperature (1-2 ˚C every five minutes) related to the hypermetabolic state (Rosenberg et al., 2015, p. 2).
- *DIC*: associated with end-stage organ failure and prolonged hyperthermia (Litman, 2019).
- *Muscle rigidity:* sustained contracture related to the increased level of intracellular Ca^{2+} in skeletal muscles (Litman, 2019).
- *Rhabdomyolysis*: the breakdown of skeletal muscle results in life-threatening hyperkalemia and myoglobinuria (Litman, 2019).
- *Cardiac arrhythmias*: frequently develop due to acute hyperkalemia (ie. ventricular ectopy, tachycardia or fibrillation) (Litman, 2019).

Implications for Nursing Care

- Treatment (Seifert et al., 2014, pp. 190-196):
  - Discontinuation of trigger agents
  - Increase oxygenation and hyperventilate
  - Dantrolene 2.5 mg/kg every five minutes
  - Cooling measures
  - Treat electrolyte disturbance
  - Treat rhythm disturbances
  - Monitor for recrudescence (24 hours)
- Dantrolene is the only drug known to treat MH (Rosenberg et al., 2015, p. 10):
  - Binds to specific sites on the RyR1 protein and reduces channel activity.
  - Available in:
    - Dantrium (20 mg vial), which requires 60 mL of sterile water to prepare.
    - Ryanodex (250 mg ampoule), which requires 5 mL of sterile water to prepare.

Clinical Resources

- Preventative measures (Rosenberg et al., 2015, pp. 11-12):
  - Preoperative assessment for a history of MH
  - Awareness of community genetics.
    - Clusters of MH cases located in Wisconsin, Nebraska, West Virginia, and Michigan (Mullins, 2018, p. 583).
  - Patients with any form of muscle disorder should receive extra anesthesia caution.
  - Patients undergoing general anesthesia should have core temperature monitoring.
  - Total intravenous anesthesia should be considered for MH suspectable patients.
  - Awareness of facility MH protocol.
- MH Carts (Seifert et al., 2014, p. 194):
  - Available in some facilities.
  - Contains all the necessary supplies to manage an MH crisis.
- MHAUS Hotline (Seifert et al., 2014, p. 194):
  - (800) 644-9737
  - National hotline is available for instruction.

Current Research

- Magnesium (Mg^{2+}) in MH treatment (Choi, Koenig, & Launikonis, 2017).
  - The research concluded that the administration of dantrolene in the presence of higher levels of Mg^{2+} is more effective than normal, resting Mg^{2+} levels.
  - Dantrolene increases the affinity of the RyR1 channels for free Mg^{2+}.
  - Free Mg^{2+} helps suppress Ca^{2+} release from the RyR1 channels. Thus, decreasing intracellular Ca^{2+} accumulation in skeletal muscles.

Conclusion

Despite the rarity of MH, the genetic condition must be thoroughly understood by all health care professionals that interact with patients who are exposed to anesthetic gases and succinylcholine. The providers must be vigilant to certain signs and symptoms and be ready to respond quickly.

MH crisis requires specific interventions within certain time frames. The awareness of MH protocol and treatment allows providers to deliver optimal care in emergencies. Team training, simulation, and case studies are important in preparing health care members for an MH emergency.

By understanding the pathophysiological process of MH, providers can differentiate symptoms of MH from other pathologies. Comprehension of MH at the cellular level aids in the knowledge of MH treatment interventions.

References Cited

Additional Sources

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