Emergent Management of Malignant Hyperthermia: Review article

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**ABSTRACT**

**Background:** Malignant Hyperthermia (MH) is a highly uncommon and potentially serious medical condition. It presents as an emergency crisis and can occur as a reaction to some anesthetic drugs but it is curable. Malignant Hyperthermia (MH) is a genetic disorder affects the homeostasis of myoplasmic calcium in skeletal muscle cells. Malignant Hyperthermia reactions, which can be triggered by agents like succinylcholine and halogenated anesthetic gases, can be seen in individuals who are genetically susceptible to them.

**Objective:** In order to maximize therapy and reduce patient morbidity and mortality, this review concentrated on the identification and treatment issues of MH in the emergency room.

**Methods:** PubMed, Google scholar and Science direct were searched using the following keywords: Malignant hyperthermia, Emergency crisis and Management. The authors also screened references from the relevant literature, including all the identified studies and reviews, only the most recent or complete study was included between 1984 and 2020. Documents in a language apart from English have been excluded as sources for interpretation. Papers apart from main scientific studies had been excluded (documents unavailable as total written text, conversation, conference abstract papers and dissertations).

**Conclusion:** Malignant hyperthermia is an uncommon but serious emergency. Over the past few years, the chance of dying from MH has grown. An experienced anesthesiologist who is careful and attentive can spot the warning indications of an approaching MH reaction and administer treatment right away to prevent the dangerous condition's consequences. The early identification and treatment are essential for the effective management. The onset may occur minutes after induction or it may be sneaky. Early Malignant Hyperthermia (MH) symptoms are frequently non-specific, which can make a diagnosis exceedingly challenging.

**Keyword:** Malignant Hyperthermia, emergency crisis, skeletal muscle cells, the homeostasis of myoplasmic calcium.

Introduction

The therapeutic management of a predominance of "regular" cases and of the occasional notable cases, with only infrequent encounters of extreme cases with potentially fatal outcomes, characterizes the medical practice in general. Few physicians will ever really care for a patient experiencing malignant Hyperthermia (MH) throughout their training or even over the course of their whole career because the prevalence of this potentially fatal condition is relatively low [1]. Between 1:5,000 and 1:50,000–100,000 anesthesia, MH responses occur. The prevalence of the genetic anomalies, however, may be as high as one in 3,000 people. Humans and some

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Animal like dogs, horses, and presumably other animals are all impacted by MH [2]. Malignant Hyperthermia appears as a potentially fatal hypermetabolic crisis that can cause muscle cell disintegration, hyperkalemia, acidosis, a rise in the serum concentration of creatine kinase (CK), and myoglobinuria. MH complications can result in cardiac arrhythmia, cardiac arrest (caused by acidosis and hyperkalemia), renal failure, compartment syndrome, pulmonary edema, and damage to the central nervous system [3]. Molecular genetics will be utilized more frequently to identify persons at risk as the sensitivity of genetic testing rises. Dantrolene sodium should be provided wherever general anesthesia is used since it is a particular antagonist of the pathophysiologic alterations of MH. Less than 5% of people still die from MH now, compared to more than 80% thirty years ago [2]. In order to maximize therapy and reduce patient morbidity and mortality, this review concentrated on the identification and treatment issues of MH in the emergency room. Patients should be monitored for at least 24 hours after the reaction because there is a chance of recrudescence. Survivors and their family members should be directed to a specialized mental health center for additional testing and counselling because it is a genetic disorder [4, 5].

**Etiology**

Patients who are genetically predisposed to the condition may experience malignant hyperthermia in response to stresses including strenuous exercise and high temperatures, as well as triggering substances like succinylcholine and/or halogenated anesthetic gases. Despite being inhaled anesthetics, nitrous oxide and xenon are not halogenated and have not been linked to malignant hyperthermia [4]. Disruption of the excitation-contraction coupling is the mechanism of malignant hyperthermia, which leads to increasing calcium ions ($\text{Ca}^{2+}$) released from the sarcoplasmic reticulum through the $\text{Ca}^{2+}$ release channel of the skeletal muscle sarcoplasmic reticulum (RyR1) in response to the triggers [6, 7]. It appears as a potentially fatal hypermetabolic crisis that can cause the destruction of muscle cells, hyperkalemia, acidosis, a rise in the serum concentration of creatine kinase (CK), and myoglobinuria [8, 9].

**Epidemiology**

In every region of the world, malignant hyperthermia (MH) affects all ethnic groups. Between 1:10,000 and 1:250,000 anesthetics, MH episodes occur often under anesthesia. Even though those substances that are known to cause MH episode may cause MH crisis with the first exposure to anesthesia, patients typically need three anesthetics before triggering [10]. Males have reactions more commonly than females in the rate of 2:1. 45 to 52 percent of observed cases involve individuals younger than the age of 19 [2]. With the introduction of dantrolene sodium for the treatment of MH, the mortality rates dropped dramatically from 70-80% to 10%. More recently, mortality is estimated to be less than 5% with early detection of MH episodes using capnography, prompt use of the drug dantrolene, and the introduction of diagnostic testing. Although MH has low mortality rates, it has substantially higher rates of morbidity. The morbidity rate of MH is 34.8%, and frequent complications include changes in consciousness level/coma (9.8%), cardiac dysfunction (9.4%), pulmonary edema (8.4%), renal dysfunction (97.3%), disseminated intravascular coagulation (7.2%), and hepatic dysfunction (5.6%) [10, 11]. Although the type of anesthesia was not specified, a survey of 12 million hospital discharges in the state of New York revealed that the prevalence of MH was one in 100,000 surgical procedures. This most likely shows a reduction in MH in relation to general anesthesia [12].

**Causes**

Due to a genetic abnormality, the muscle cells of individuals who are more susceptible to malignant hyperthermia have abnormal proteins. A change in the DNA sequence is referred to as a genetic mutation. Cells receive the information they require to carry out their functions from DNA sequence. Patient might exhibit signs of a genetic disorder if part of DNA sequence is incomplete or damaged. While, this mutation does not normally manifest any symptoms, it can result in an irregular calcium release from muscle cells when patients are exposed to some anesthetics, extreme heat, or vigorous activity [12, 13]. Consistent muscular contraction (tight or inflexible muscles) and an abnormal rise in metabolism and body temperature are the results of this. Eventually, muscle cells decay and release a lot of potassium into the blood, which results in more symptoms and disorders. When a person who is genetically predisposed to the disorder is exposed to specific inhaled or intravenous anesthetic drugs, malignant hyperthermia may result. Among the drugs that can be inhaled include halothane, desflurane, sevoflurane, and isoflurane. Succinylcholine is one of the drugs used intravenously (fast-acting muscle relaxant) [12]. There are other different genes that cause malignant hyperthermia susceptibility (MHS). Gene RyR1 is the most often affected gene. CACNA1S and STAC3 are
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two genes that are affected less frequently [13, 14].

**Risk factors**
If there is family history of genetic condition of Malignant Hyperthermia Susceptibly (MHS), risk of developing it is increased. To be affected by this illness, just one altered gene from a parent must be inherited (autosomal dominant inheritance pattern). There is 50% risk of developing Malignant Hyperthermia Susceptibly (MHS), if one of parents carries the gene mutation that causes it. Risk of having MHS is further raised if patient have other family members who do. Additionally, having one of the following conditions increases risk of developing malignant hyperthermia like a history of an incident that may have caused malignant hyperthermia, while under anesthetics or a history of rhabdomyolysis, a condition in which exercising in conditions of high heat and humidity or using a statin medicine can cause the breakdown of muscle tissue or specific muscle conditions and illnesses brought on by inherited gene alterations [15].

**Diagnosis**
Only a tiny percentage of malignant hyperthermia (MH) patients are currently reported to involve emergent MH reactions, which manifest with the entire set of rapidly rising clinical symptoms of MH (hypercarbia, tachycardia, hyperthermia, acidosis, and muscle rigidity) [13]. The onset of the first clinical signs is frequently delayed and they are more insidious in cases of MH that have recently been documented [14]. Many of these patients, who were subsequently identified as being MH susceptible, show that the symptoms can go away after stopping the triggering anesthetics but before dantrolene is given [15, 16]. Signs and symptoms, observation during and promptly after anesthesia, and blood tests to identify complications are used to determine the diagnosis of malignant hyperthermia. The early warning symptoms of malignant hyperthermia are unexplained increasing heart rate (tachycardia). Unexpected rise in the amount of carbon dioxide, which the body produces, tachypnea (Quickly breathing), muscle stiffness and rapid temperature increase [17]. The Later diagnostic features of malignant hyperthermia are dark urine, an elevation in body temperature that is greater than that associated with a fever (hyperthermia), blood testing revealing muscle breakdown, rhythmic heart disorders, bleeding and seizures [13].

**Testing for susceptibility:** If there are risk factors, testing to determine whether patient have a higher risk of developing malignant hyperthermia (susceptibility testing) may be advised. Tests might involve a muscle biopsy or genetic analysis [7].

**Muscle biopsies (contracture test):** In some situations, if patient at risk for malignant hyperthermia, doctor might advise a muscle biopsy test. A little part of muscle tissue is surgically extracted and sent to the lab for examination. To assess how the muscle contracts, the specimen is subjected in the lab to agents that cause malignant hyperthermia. Travel to a dedicated muscle biopsy facility is required since this test must be performed on muscle tissue right away after it has been removed [18].

**Genetic analysis:** Genetic testing identifies the gene change (mutation) that predisposes to malignant hyperthermia. Blood is drawn, sampled, and transported to a lab for evaluation. A gene alteration that indicates have the hereditary illness known as malignant hyperthermia susceptibility (MHS) can be found through genetic testing [19, 20].

**Management of Malignant Hyperthermia**
As soon as an MH crisis is suspected, get therapy. Treatment adjustments should be made in accordance with how MH presents clinically. To treat the symptoms-only: First consult the Malignant Hyperthermia Investigation Unit in the area for more information. Then, immediately put an end to all triggers, use 100% O2 at high flow to hyperventilate (use a minute volume 2-3 times normal), after that call for medical help and declare an emergency. Change over to non-trigger anesthesia (TIVA). Inform the physician and request that the operation be stopped or postponed. Instead of wasting more time changing the circuit or anesthetic machine, disconnect the vaporizer [21].

**Dantrolene**
If an anesthesiologist suspects Malignant Hyperthermia, the main treatment for malignant hyperthermia is to deliver dantrolene right away. Additionally, they stop administering the triggering anesthetics, and the surgeon quickly completes the procedure. The dose of dantrolene is 2 mg/kg taken by injection I.V. (Mix ampoules of 20 mg with 60 ml sterile water). An adult patient might require at least 36 to 50 ampoules. Dantrolene infusions needs to be repeated until the respiratory and cardiac systems become stable. There may be a need to go over the recommended dosage (10 mg kg-1) [22].

**Monitoring**
Maintain standard anesthesia monitoring (SaO2, ECG, NIAP, and e’CO2) as usual. Check the internal body temperature and create effective IV lines using wide-
bore cannulas. Then, consider placing a urinary catheter, an arterial line, central venous line and obtain samples for the testing of myoglobin, glucose, arterial blood gases, K+, and CK. After that, check the coagulation, kidney, and liver functions. At the end, look out for compartment syndrome symptoms and keep an eye on the patient for at least 24 hours (ICU, HDU, or in a recovery unit). Also, 2000 – 3000 ml of IV 0.9 percent saline at 4°C refrigeration. Surface cooling methods include fans, ice packs and cold. Damp sheets placed on the groin and axillae are used and any further cooling tools. Upon reaching 38.5°C, stop cooling [15].

**Treatment for Hyperkalemia**

To treat the hyperkalemia, give 50 percent dextrose in 50 ml with 50 IU of insulin (adult dose) and 0.1 mmol/Kg intravenously from CaCl₂ (7 mmol=10 ml for adult weighing 70 kg). Dialysis might be needed. Treatment for acidosis by normocapnic hyperventilating. If the pH is less than 7.2, provide sodium bicarbonate intravenously. Treatment for arrhythmias by giving amiodarone [dosage for adults is 300 mg (3 mg/kg/min)] and β-blockers (such as propranolol, metoprolol, and esmolol), if the tachycardia doesn’t go away. Urine output should be kept at least 2 ml per kilograms each hour (0.5 – 1 mg/kg of furosemide and mannitol 1 g/kg). Crystalloids, such as intravenous lactated Ringer’s solution or 0.9 percent saline fluids. Patients who may be susceptible to malignant hyperthermia (MH) should get tested for it [15].

**Complications**

Malignant hyperthermia has the potential to cause serious issues, including: An uncommon disorder that results in the degeneration of muscle cells (rhabdomyolysis, renal failure or damage, clotting and bleeding issues or Death [20]. Unless patients are aware of the genetic mutation that causes malignant hyperthermia or have informed anesthesiologist about a family history of the disorder, malignant hyperthermia is impossible to prevent. Anesthesiologist won’t use the known triggers for anesthetic plan if this is the case. Sadly, most people are unaware that they are at risk for malignant hyperthermia until it affects them [21]. To evaluate the risk of malignant hyperthermia, anesthesiologist should be consulted to avoid certain anesthesia drugs [22, 23]. Exercise in extreme heat and humidity could result in another reaction if already suffered from malignant hyperthermia as a result of specific anesthetic medicines. Any precautions to be taken should be discussed with physiotherapist. Ask doctor if genetic testing is necessary to find out if have a hereditary condition that increases risk of developing malignant hyperthermia. Ask if members of the close family should think about getting tested genetically. This informs medical professionals of danger, particularly in an emergency when might not be able to speak [24, 25].

**Conclusion**

Malignant hyperthermia is an uncommon but serious emergency. Over the past few years, the chance of dying from MH has grown. An experienced anesthesiologist who is careful and attentive can spot the warning indications of an approaching MH reaction and administer treatment right away to prevent the dangerous condition's consequences. The early identification and treatment are essential for the effective management. The onset may occur minutes after induction or it may be sneaky. Early Malignant Hyperthermia (MH) symptoms are frequently non-specific, which can make a diagnosis exceedingly challenging.

**Conflict of Interest**

None

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None

**References**


