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# Malignant hyperthermia – state of knowledge

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## Abstract

Malignant hyperthermia (MH) is a relatively rare, but potentially lethal genetic disorder. That disease is characterized by hypermetabolic response of the skeletal muscles caused by exposure to triggering agents e.g. volatile anesthetics or depolarizing neuromuscular blockers.

The object of this article was to review and assess the most recent published works about the epidemiology, etiology, pathomechanism, therapy of the MH and the new advances in all these fields.

Authors scrutinized PubMed and Google Scholar using keywords: malignant hyperthermia, volatile anesthetics, ryanodine receptor mutation. In addition to this, the references of chosen articles were manually scoured for supplementary applicable articles. The literature was selected on the basis of a general medicine readership and prioritized clinical practice guidelines, systematic reviews and case reports.

The references include the latest reports on malignant hyperthermia, apart from works of historical importance.

Available treatment methods consist mainly of pharmacotherapy, symptomatic treatment and monitoring of vital parameters. Dantrolene is a first-choice drug in initial treatment of MH and is considered the only specific antidote.

In spite of the constant advances in the areas of medicine there is still much to be discovered about MH. Further studies are necessary, as the amount of credible evidence is not adequate.

Keywords: malignant hyperthermia, ryanodine receptor, succinylocholine, anesthetics

## Introduction

Malignant hyperthermia (MH) is a relatively infrequent, but possibly mortal condition that patients can experience during the perioperative phase.[1] MH is considered as a myopathy without manifestation of any characteristic clinical symptoms.[2] It is usually triggered by a volatile anesthetics (sevoflurane, isoflurane, halothane), depolarizing muscle blockers (succinylcholine) and very rarely to a stressors such as dynamic training and heat.[3]

Manifestations of MH are unspecific and arise as a result of hypermetabolic activity: increased $CO_2$ production, increased body temperature, muscle stiffness, rapid breathing, tachycardia, metabolic acidosis, hyperkalemia and rhabdomyolysis. The symptoms have quick onset, hereof, immediate diagnosis and proper treatment are crucial in preventing mortality.[4]

The very first reports in the literature describing a condition that could correspond to MH were reported by several scientists on a single page in the JAMA in 1900.[5] However it wasn't until 1962, when the Denborough came up with the major breakthrough in discovering that MH is a genetic disorder.[6] This thesis was further developed and confirmed by Britt in 1969 and the other researchers.[5]

## Epidemiology

The prevalence of MH is estimated at 1:15000 to 1:75000 anesthesia procedures and occurs regardless of race and gender.[3,7,8] However, the frequency of MH genetic feature is rated at 1:2000 to 1:3000, which is significantly higher than the actual number of MH clinical incidences.[7,9,10] In view of the fact that the MH genetic features are very diverse and not fully infiltrated, its true prevalence is likely underestimated. Like previously mentioned, MH symptoms might not be specific and can be undiagnosed. Moreover, patients suspected of MH genetic features may undergo several (three on average) surgeries without developing fully symptomatic MH reaction.[7,11]

In the past, the mortality rate of MH was high, reaching as much as about 70%. After introducing dantrolone as an antidote drug, the mortality rate of MH was reduced to less than

5%. Regardless of the significant reduction of lethal cases, the morbidity rate was reported as high as 34.8% by Larach et al. in 2010.[12,13]

**Etiology and pathomechanism**

Malignant hyperthermia (MH) is described as a pharmacogenetic ailment.[3] Its etiology depends on many factors and the major of them appears to be an autosomal gene mutation.[1] Due to this malignant hyperthermia makes an appearance because of abnormal structure and function of some specific proteins.[14] The most frequently described altered receptor linked to this condition is RyR1 – ryanodine receptor type 1, whose gene (*RYR1*) is located on chromosome 19q13.1.[3,14,15] This receptor occurs in skeletal muscles. Abnormalities associated with this locus are estimated to perform between 1:2000 to 1:3000 but the incident rate of abnormalities related to malignant hyperthermia is 1:2750.[3,9] More than half of the family members of the patients with malignant hyperthermia have MH-associated variants of *RYR1* gene within different populations.[9,16] Other anomalies of RyR1 are associated with diseases such as congenital fiber type disproportion, centronuclear myopathy and bleeding abnormalities.[17]

Another gene mutation associated with malignant hyperthermia is the mutation of *CACNA1S*, which is in charge of alpha-1 subunit of the dihydropyridine receptor, also known as T-tubular voltage gated $Ca^{2+}$ channel ($Ca_v$).[9,18] Both RyR1 and $Ca_v$ are components of the skeletal muscle excitation-contraction coupling complex. It appears on the sarcoplasmic reticulum. Any mutation of *CACNA1S* or *RYR1* can be a cause of channelopathies of the complex.[19] *CACNA1S* abnormalities cause only approximately 1% of malignant hyperthermia cases in contrast to *RYR1* abnormalities which cause up to 70% of those cases.[20] Other mutations of *CACNA1S* are associated with illnesses such as thyrotoxic periodic paralysis type 1 and hypokalemic periodic paralysis type 1.[19]

Another gene mutation that has been found in the Lumbee Native American population of North Carolina involves *STAC3*, which is located on chromosome 12q13-14.[21] It is in charge of cysteine-rich domain 3 (STAC3) and it is considered to be a vitally important chaperone of essential protein complexes in skeletal muscles.[3,19] Abnormalities of *STAC3* may also be linked with congenital myopathy, palate anomalies, musculoskeletal anomalies and micrognathia.[22]

Malignant hyperthermia may also be caused by mutations of other genes, such as *CACNB1*, *KCNA1*, *CASQ2*, *SERCA1*, *CASQ1* because of their engagement in calcium homeostasis. Currently those connections are assumptions so it requires further studies to prove those relations.[9]

Heat production is connected directly with high levels of intracellular $Ca^{2+}$ . The enhanced level of the molecule results in unusual muscle metabolism, increasing ATP hydrolysis oxygen consumption and CO 2 production [1]. Declining levels of ATP are influencing $Ca^{2+}$ -ATPase which can't control arrangement of $Ca^{2+}$, presumably leading to the failure of membrane integrity. To sum it all up, defects of channels transporting $Ca^{2+}$ are strictly connected to malignant hyperthermia susceptibility, especially an altered Ryanodine receptor.[3,14]

**Symptoms**

This condition is characterized by a sudden rise in body temperature, rhabdomyolysis, and, at its most advanced stage, decay and death.[23] It is much more common in susceptible individuals with an autosomal dominant mutation.[23,24] It can be described as

a hypercatabolic syndrome of skeletal muscles, most often caused by inhaled anesthetics or muscle relaxants cause a rapid disconnection of oxidative phosphorylation.[23,25]

Diagnosis is based on clinical symptoms of hypercapnia, tachycardia, muscle breakdown, hyperthermia, cardiac arrhythmias, and laboratory abnormalities (metabolic acidosis, hyperkalemia, elevated levels of creatinine kinase and serum and urine myoglobin).[1,23]

The susceptibility of the subjects is also determined by the in vitro contracture test and the genetic test for RYR1, CACNA1S and STAC3 gene variants.[23] The in vitro contracture test (IVCT) involves taking a fragment of a vastus lateralis or biceps brachii muscle. The sample is then treated with halothane or caffeine and fluctuations in muscle tone are measured.[26–29]

The most important symptoms are hyperthermia, tachycardia, arrhythmia, rhabdomyolysis, metabolic and respiratory acidosis, cyanosis, lactic acidosis, coagulopathy, hyperkalemia, and renal failure.[1,25] In the initial stage, there is a rapid decrease in the amount of ATP, which results in increased CO2 production, respiratory acidosis, increased body temperature and increased demand for oxygen. The second stage of symptoms results from the depletion of ATP reserves - metabolic acidosis and lactate formation occur. If the diagnosis is too late, it leads to multi-organ failure, cardiac arrhythmia, tachycardia, renal failure, and intravascular coagulation syndrome (DIC).[30]

The MH episode is most often fatal (up to 80% of cases), but drops to 5% after a quick and accurate diagnosis and the use of dantrolene sodium.[25] Anesthesiologists are required to recognize the signals indicating the onset of MH and to make an accurate and prompt diagnosis.[26,31]

In practically all cases, the first symptoms of MH develop already in the operating room (tachycardia, tachypnea). Nevertheless, MH may also occur in the initial postoperative period. Single cases of MH occurrence during exercise and / or exposure to a hot environment have also been reported.[32] The increase in internal body temperature increases by 1-2°C every five minutes up to 44°C.[33] MH can also lead to heart failure, intestinal ischemia, cramped limbs syndrome as a result of deep muscle swelling, pulmonary edema, renal failure, coma, liver dysfunction, and cerebral infarctions.[13,33,34]

The literature describes the case of a 49-year-old man who attempted suicide with chlorfenapir, and then developed MH after intubation.[23]

A case of a 5-year-old male subject undergoing a living donor kidney transplant due to end-stage renal disease has been described. In the interview, it was reported that the patient was repeatedly exposed to anesthetics and that there were no complications. However, after reperfusion, a fulminant course of MH developed with hyperthermia, hypercarbia, tachycardia, and muscle stiffness.[35]

## Treatment

Because of life danger during the Malignant Hyperthermia crisis, treatment should be started as fast as MH is suspected. First step during crisis is calling for help and immediate change MH-triggering anesthetic, to a non-MH-triggering anesthetic (*eg. Nitrous oxide*).[36] Next step should include hyperventilation with 100% oxygen, cooling and requesting to abort the surgery.[31,37]

*Tab. 1 Safe and forbidden medicaments for people with diagnosed or susceptibility for MH.*[3,31,36,38,39]

| MH-triggering anesthetics | non-MH triggering anesthetics |
|---|---|
| 1. ether<br>2. halothane<br>3. enflurane<br>4. isoflurane<br>5. sevoflurane<br>6. desflurane<br>7. succinylcholine | 1. propofol<br>2. cetamine<br>3. etomidate<br>4. benzodiazepine<br>5. barbiturane<br>6. opioids<br>7. nitrous oxide<br>8. nondepolarizing skeletal muscle relaxant (eg. tubocurarine)<br>9. local anesthetics |

If MH occurs, dantrolene should be administered instantly. Dantrolene sodium is the only antidote for MH.[1] There are two main dantrolene preparations available: Dantrium®, in 20 mg vials which require 60 ml of sterile water to prepare, average adult require from 8 to 10 ampoules and Ryanodex®, newer alternative approved by the FDA, available in 250 mg ampoules, which require only 5 ml of sterile water. Ryanodex® is more soluble than Dantrium®, and only one ampoule of Ryanodex can achieve an aim of the treatment.[40]

Patients after MH, who received dantrolene sodium, should be monitored closely for 48-72h, because 25% of them can experience a recurrence of the syndrome.[41] In addition, test for DIC should be included.[3] Some cases show, that there is a potential for CPB (Cardiopulmonary bypass) or ECMO (extracorporeal membrane oxygenation) to treat the symptoms of MH.[42]

*Tab. 2 Recommended solution in case of suspected MH crisis based on European Malignant Hyperthermia Group recommendation.*[31,39]

| Casual treatment | Symptomatic treatment |
|---|---|
| 1. Discontinuation of anesthetics<br>2. Beginning hyperventilation 100% $O_2$ >10 L $min^3$<br>3. Calling help<br>4. Aborting the surgery<br>5. Conversion or safe analgetics<br>6. Removing evaporator<br>**7.** Administration dantrolene (max. 10 mg/kg) | 1. Physical cooling<br>2. Correction of hyperkalemia<br>3. Correction of acidosis<br>**4.** Treatment of heart arrhythmia |
| **Monitoring** | |
| 1. ECG, $SpO_2$, $etCO_2$, BP, RR<br>2. temperature<br>3. gasometry<br>4. creatine, phosphokinase, myoglobin, glycemy<br>5. coagulation profile<br>6. duresis<br>**7.** arterial line | |

**Summary**

Malignant hyperthermia still remains a pertinent clinical condition in anesthesia, which, without proper management, could have dire consequences. Discovery and introduction of dantrolene into protocole of MH treatment contributed significantly to decreasing mortality rate. Further advances in the field of anesthesiology and the pharmaceutical industry give perspective views to discovering more non-MH triggering anesthetics and drugs. Development in the fields of genetic testing and diagnostic methods have brought huge amounts of data and information about the genetic traits in charge of MH incidents.

The mutual target is to improve alertness in recognizing MH, what may enable quick reaction and implementation of appropriate treatment. Taking the right action at the right time can make a measurable contribution to improving efficiency in treatment that brings mortality rate close to zero.

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