Towards A Definition Of Malignant Hyperthermia And Mh-like Syndromes

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My opinion

Malignant Hyperthermia (MH) is a life threatening syndrome characterized by hypermetabolism, hyperthermia, acidosis, muscle contraction, muscle membrane breakdown, hyperkalemia and rhabdomyolysis. The syndrome occurs as a result of exposure to certain drugs and/or environmental conditions. All the signs of MH may appear together or in some combination. The onset and course of the syndrome is variable as well. The underlying cause of MH is thought to be an abnormal, uncontrolled, elevation of intracellular calcium in skeletal muscle cells. Dantrolene sodium effectively reverses the syndrome by restoring calcium levels in the cell toward normal.

Because there are may be many causes of elevated intracellular calcium, and since there are a variety of clinical presentations of MH and conditions that resemble MH(MH-like syndromes), I suggest subtyping the expression of MH and MH like syndromes. This classification is meant to serve as a framework for thinking about different clinical situations that are often lumped together under the name Malignant Hyperthermia. What follows is my extrapolation from experimental data and clinical studies.

MH related to anesthesia

I believe that this is the most common form of MH. Based on sequencing of the DNA of the ryanodine receptor gene(RYR-1), 60-70% of patients who develop MH upon exposure to potent inhalation agents and/or the paralyzing drug succinylcholine will be found to have a mutation in this gene. However, only about 30% of these mutations have been proven to be causal for the MH syndrome(1), as most of the others have not yet been functionally evaluated. In about 2% of the MH susceptible population a mutation is found in another gene, the dihydropyridine (DHPR) gene(2). Both the RYR-1 and the DHPR gene mutations result in a structural and/or functional change in ryanodine receptor calcium channel activity that promotes increased calcium release from the storage site for this ion in the cell,( the sarcoplasmic reticulum,) and probably increased calcium entry into the cell upon exposure to the agents mentioned above.

In addition, two muscle disorders (myopathies)characterized by muscle weakness, Central Core Disease and Multiminicore Disease, have as their basis mutations in the RYR-1 gene(see the section on myopathies and MH) and predispose most of these patients to MH

MH signs unrelated to anesthetic agents with abnormal RYR 1/DHPR genes

Patients with mutations in the RYR-1 gene may also present with the signs and symptoms of MH when exposed to drugs and environmental conditions that produce elevated intracellular calcium levels other than inhalation agents/succinylcholine. In animals who are MH susceptible and also have RYR-1 mutations elevated temperature leads to increased calcium release from the sarcoplasmic reticulum stimulates the enzymatic induction of compounds called reactive nitroso intermediates. These compounds, in turn alter the mutated ryanodine receptor resulting in uncontrolled calcium release, muscle contraction, increased heat production and a vicious "feed-forward" cycle of more calcium in the cell, increased production of reactive intermediates resulting in all the signs of MH(4)

Exercise and muscle exertion may also precipitate muscle breakdown and even clinical MH.(5) This has been demonstrated in MH susceptible pigs and in genetically engineered mice that harbor a causal MH mutation in the RYR-1 gene(6) but the pathophysiology remains unknown.

Statins, free fatty acids, caffeine, serotonin and MDMA agonists also promote abnormal calcium release from the SR in isolated muscle and sarcoplasmic reticulum preparations with RYR-1 containing MH mutations. (7-12). With sufficiently high concentrations and in combination these agent may induce sufficiently elevated intracellular calcium to precipitate an MH crisis.

The Neurolept Malignant Syndrome (NMS) is a syndrome precipitated by a variety of agents that are used to treat psychiatric disorders. In a few patients who developed NMS an MH-causative RYR-1 mutation has been identified(7). This has been termed the Neuroleptic-Induced Malignant Hyperthermia Syndrome (NIMHS) and is characterized by muscle rigidity, fever, high respiratory rate, elevated serum creatine kinase and rhabdomyolysis(7)

Of the MH gene mutations, about 90% are in the RYR-1 gene, however, the DHPR gene is also implicated in some cases of MH. Some patients who carry mutations in both the RYR-1 and DHPR genes may present with MH-like signs and symptoms in the absence of inhalation agents/succinylcholine or the paralyzing drug succinylcholine,

Contrary to popular belief, the MH gene mutations identified in susceptible animals do not cause MH in all instances. Indeed, the MH gene mutations can be found in non-susceptible animals and even in normal individuals. In animal studies, the MH gene mutations can be found in non-susceptible animals and even in normal individuals. In animal studies, the MH gene mutations have been found to enhance and accelerate the MH crisis when introduced into non-susceptible animals that were exposed to the inhalation anesthetic agents and succinylcholine that are known to precipitate the MH crisis in normal susceptible animals.
mutation has been identified (13) but others do not seem to have such mutations. In a few patients an apparent MH crisis has occurred without exposure to anesthetic trigger agents or the drugs mentioned above. The circumstances that “trigger” the syndrome remain to be clarified.(14)

MH with normal RYR-1 gene.
Elevated intracellular calcium may occur without apparent structural change in the ryanodine receptor as well. For example, exposure to a combination of several calcium releasing agents (mentioned above) that individually do not lead to high enough calcium concentrations to initiate the biochemical changes of MH may result in calcium levels high enough to produce signs of an MH-like syndrome. This has been demonstrated in pre-clinical animal studies and likely in humans.(15,16,17).

MH due to absence/reduction of Calcium binding proteins
Yet another potential mechanism for elevated intramyoplasmic calcium is the absence or reduction of proteins that buffer the concentration of calcium in the sarcoplasmic reticulum. In the absence of such buffering proteins, such as calsequestrin, marked elevation of intracellular calcium sufficient to cause signs of MH may occur when the muscle is exposed to agents that cause calcium release from the sarcoplasmic reticulum.

This phenomenon has been demonstrated in mice that have been genetically engineered to lack production of calsequestrin (18,19). However, as of now no cases of MH resulting from the absence of these calcium buffering proteins have been reported in humans.

Since mitochondria also play a role in calcium homeostasis in the cell it has been speculated that abnormal mitochondrial function may lead to elevation of intracellular calcium sufficient to induce signs of MH(20).

MH and myopathies
Mutations in the RYR-1 gene are also causal for two muscle disorders, Central Core Disease and Multiminicore disease. The disorders are characterized by weakness and structural changes in the muscle in the absence of anesthesia. Patients with these disorders are likely to develop MH on exposure to MH trigger agents.(1)

Certain myopathies not related to mutations in the RYR-1 gene may either directly or indirectly, lead to increased myoplasmic calcium levels upon exposure to calcium releasing agents such as inhalation anesthetic agents. Patients with Duchenne or Becker Muscular Dystrophy display weakness at an early age. Intracellular calcium is elevated in these patients. In a mouse model for Duchenne Muscular Dystrophy, Bellinger and colleagues(21) have shown that increased cellular calcium leads to production of reactive nitroso compounds which leads to “leaky” ryanodine receptors as explained above. Although not directly demonstrated in the mouse model since the animals were not anesthetized it may be hypothesized that the addition of calcium releasing agents such as halothane or other volatile anesthetics and/or succinylcholine induce signs similar to those found in MH(21). This might be the mechanism for the well known phenomenon of muscle breakdown, increased serum potassium when some Duchenne Muscular Dystrophy patients are anesthetized with MH trigger agents (22). On the other hand it is not at all clear if dantrolene can reverse these changes.

This discussion leads to a classification of MH and MH-like syndromes that seek to relate clinical signs to underlying biochemical changes and triggers of MH.

Subtypes of MH.
For purposes of this discussion, the clinical MH syndrome is defined according to the generally accepted Clinical Grading Scale (23) as likely, very likely and almost certain MH(D4, D5,D6). For this proposed re-classification of MH and MH-like syndromes, only those subtypes are termed MH where the RYR-1 or DHPR gene is mutated. The other subtypes are best described as “MH-like”.

MH Syndromes
Type 1: Mutations in RYR-1 /DHPR or other genes that are implicated in calcium release from the sarcoplasmic reticulum together with exposure to volatile anesthetics and/or succinylcholine. That is classical MH. This might be labeled as Denborough syndrome in recognition of the scientist who first brought the syndrome to the world’s attention.

Mutations in the RYR-1 gene causal for Central Core Disease or MultiMinicore Disease are included in this category.

Type 2: Mutations in RYR-1 /DHPR or other genes that are implicated in calcium release from the sarcoplasmic reticulum and exposure to non anesthetic drugs/agents or environmental conditions that promote calcium release such as high environmental temperatures. This might be labeled as Britt syndrome in recognition of Dr. Britt’s early work on the description of the syndrome.

MH-Like Syndromes
Type A. Normal RYR-1 in combination with two or more sarcoplasmic reticulum calcium releasing agents, e.g. caffeine, halothane, heat.

Type B. Normal RYR-1/DHPR and increased calcium due to decrease in sarcoplasmic reticulum calcium buffering proteins

Type C. Normal RYR-1/DHPR in a patient with a myopathy following exposure to calcium releasing agents. For example, Duchenne or Becker’s Muscular Dystrophy patients who receive MH trigger agents.

Conclusion

The Malignant Hyperthermia syndrome is a unique pharmacogenetic disorder. Although potent volatile anesthetic gases and succinylcholine were thought to be the only triggers for the syndrome, with clarification of the pathophysiology of MH, it has become apparent that the abnormal function of the ryanodine receptor may be induced by a variety of medications as well as environmental stimuli.

There is much to be learned about the phenotype-genotype relationships of those who are MH susceptible and others who harbor abnormalities of the ryanodine receptor.

Abbreviation(s)

MH-malignant hyperthermia
Ryr-ryanodine receptor
NMS-neuroleptmalignant syndrome
DHPR-dihidropyridine receptor
MDMA-3,4-Methylenedioxyamphetamine

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