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Malignant Hyperthermia: A Review of Clinical Phenotype and Molecular Genotype

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Malignant hyperthermia (MH) is a rare inherited skeletal muscle disorder related to general anaesthesia. It is primarily caused by a mutation in the RYR1 gene. The RYR1 gene codes for the ryanodine receptor 1, which is responsible for calcium release in skeletal muscle. An episode of malignant hyperthermia is typically triggered by volatile anaesthetic agents such as halothane, isoflurane, desflurane, etc, depolarising skeletal muscle relaxants such as succinylcholine, and caffeine which cause contractures in skeletal muscles. These contractures are enhanced when calcium reuptake is inhibited in the sarcoplasmic reticulum. Exposure to a triggering agent causes a substantial increase of intracellular calcium, which results in a massive, life threatening, hypermetabolic response.

There are presently over 40 known mutations in the RYR1 gene, which is on the long arm of chromosome 19. Most of these mutations are found on three major regions, *malignant hyperthermia/central core disease susceptibility* regions I, II, and III. Additionally, the CACNA1S gene mutation plays a similar role in malignant hyperthermia. This gene is found on the long q arm of chromosome 1 and most of these mutations are found at position 32.1.

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The likelihood that a patient will develop malignant hyperthermia on exposure to a triggering agent is determined on a universal points system, ranging from 0 (not likely to develop MH) to 6 (almost certain to develop MH). Severity is determined by a recognised clinical grading system, the Delphi method, which incorporates clinical findings/manifestations, and uses a points system, where a higher score denotes a more severe clinical manifestation.

Keywords: Malignant hyperthermia; RYR1 gene; ryanodine receptor 1; CACNA1S gene; central core disease; Delphi method.

1. UNDERSTANDING CENTRAL CORE DISEASE AND MALIGNANT HYPERTHERMIA

Central core disease is a congenital core myopathy, which features the central area of reduced oxidative enzyme activity (core), which extends along the total length of the skeletal muscle fiber when muscle biopsy is examined. Central core disease is an autosomal dominant inherited disorder, with many cases describing mutations in the RYR1 gene. Central core disease typically presents with muscle weakness, hypotonia, and poor motor development from infancy. The severity of muscle weakness can vary from very severe (akinesia) to mild muscle weakness. Central core disease is diagnosed based on a combination of clinical findings, and a muscle biopsy positive for central cores along the entire length of the muscle fibers [1].

Malignant hyperthermia is a pharmacogenetic condition that also affects skeletal muscle cells. In individuals with the malignant hyperthermia susceptibility (MHS) trait, exposure to a triggering agent can cause a hypermetabolic response and muscle rigidity. This is the result of an intracellular calcium imbalance, causing a substantial increase in cytoplasmic calcium. Triggering agents can include volatile anesthetic agents, succinylcholine, and caffeine. It should also be noted that non-depolarising muscle relaxants, local anesthetic agents as well as other anesthetic agents such as ketamine, fentanyl and propofol are not known to be triggers for MH [2]. Malignant hyperthermia presents with masseter muscle rigidity, increased end-tidal CO2, low pH, elevated temperature, mottling of the skin, elevated serum potassium, cardiac arrhythmias, generalised oedema, renal failure, cardiac failure, disseminated intravascular coagulopathy and, if untreated, death [3]. The gold standard for diagnosis of malignant hyperthermia is the caffeine halothane contracture test (CHCT). However, due to the lack of facilities worldwide, and the necessity for patients to travel to the center for testing, molecular genetic testing is often performed as an alternative. If one of the 40+ RYR1 mutations characterised to date is detected, the patient is considered to possess the MHS trait. The common link between malignant hyperthermia and the other core myopathies is the RYR1 gene [1].

2. MOLECULAR MECHANICS OF RYR-1 AND CACNA1S GENES

The RYR1 gene encodes for the ryanodine receptor 1 (RYR-1), the receptor isoform which predominates in human skeletal muscle; it spans approximately 15.3 kb on the long arm of chromosome 19 (19q13.1); it comprises 106 exons and encodes a protein of 5,038 amino acids. RYR-1 plays a critical role in muscle contraction by mediating the release of calcium ions from the sarcoplasmic reticulum. In human skeletal muscle, the release of calcium ions from the sarcoplasmic reticulum is effected via coupling of the ryanodine receptor to the dihydropyridine receptor (DHPR). This process, often referred to as excitation-contraction coupling, mediates the conversion of electrochemical stimulus to mechanical contraction of skeletal muscle fibers. The CACNA1S gene belongs to a group of genes that are responsible for generating calcium channels. This gene is critical in transporting calcium ions into cells thus providing movement in skeletal muscles. Channels generated with this gene play an integral role in muscle contraction and activating the RYRI gene as well. There have been two mutations of the CACNA1S gene identified by researchers. The first mutation replaces the amino acid arginine with the amino acid cysteine at protein located at 1086. The second mutation replaces the amino acid arginine with the amino acid histidine on the same protein location [4]. These mutations could potentially induce channels made with the CACNAIS gene to activate the RYR1 gene inadequately following certain medication administrations (primarily anesthetics). In doing

so, an excess of the calcium channel is released, causing an abnormal skeletal muscle contraction. As a result, muscle rigidity is observed in addition to increased body temperature and a surplus of acid leading to a state of acidosis.

Mutations in the RYR1 gene are associated with multiple variations on two major core myopathies: MH and central core disease (CCD). The majority of RYR1 mutations associated with increased susceptibility to MH and/or CCD are missense mutations found in three major clusters, termed *malignant hyperthermia/central core disease susceptibility* regions I, II and III (MH/CCD I, MH/CCD II, and MH/CCD III, respectively). The MHS trait is predominantly associated with dominant mutations in MH/CCD regions I (N-terminal amino acid residues 35-614) and II (centrally located residues 2163-2458), whereas mutations arising in the c-terminal region of the RYR1gene (MH/CCD region III, amino acids 4550-4940) are more closely associated with the classical CCD phenotype. To date, over 40 missense mutations and a single amino acid deletion in the RYR1 gene have been found to segregate with the malignant hyperthermia susceptibility (MHS) trait [5].

It is understood that mutations associated the MHS trait result in alteration of the RYR1 channel structure, such that an increased ease of opening and delayed closing of the channel results in excessive release of calcium ions from the sarcoplasmic reticulum. In skeletal muscle cells, the overabundance of free calcium ions within the cytoplasm causes abnormal muscle contraction, leading to the classical finding of severe muscle rigidity in patients with MH.

3. CLINICAL BASIS FOR DIAGNOSIS OF MALIGNANT HYPERTHERMIA

Clinical diagnostic criteria for MH susceptibility correlates directly with signs and symptoms occurring during or shortly after general anaesthesia. Once MH is suspected, clinical findings are weighed based on a universal standardised point system and summed up to obtain a raw score ranging between 0-6. A raw score of 0 signifies that the MH probability is almost never/very unlikely whereas a score of 6 signifies that the patients' likelihood of having MH is almost certain. In other words, the greater the value obtained on the clinical grading scale, the greater the plausibility of a diagnosis of MH. The clinical grading scale requires the anesthesiologist to judge whether specific clinical signs are appropriate for the patient's medical condition, anaesthetic technique, and surgical procedure [6].

The standardised criteria protocol in the Clinical grading scale for MH is broken down into two categories "Clinical findings and Manifestations" using the Delphi method. Clinical findings are broken down in order of significance. Additionally, they are weighed on a point system based on the severity of the signs and symptoms present. The first category includes "Respiratory Acidosis" with a maximum score of 15. The signs and symptoms include an end-tidal CO2 > 55 mmHg and PaCO2 > 6O mmHg. The second category found is "Cardiac Involvement" with a maximum score of 3 points. Its signs and symptoms include an unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation. Next category on the list is "Metabolic Acidosis" with a maximum score of 10 points. Signs and symptoms for this includes a base deficit > 8 mEq/L, and a pH < 7.25. The next clinical finding is "Muscle Rigidity" with a maximum score of 15 point. The signs and symptoms to look for include generalised rigidity and masseter muscle rigidity. The following category includes "Muscle Breakdown" with a possible maximum score of 15 points. The signs and symptoms to observe for include a serum creatine kinase concentration > 20,000/L units, cola-coloured urine, excess myoglobin in urine or serum and a plasma [K+] > 6 mEq/L. Next on the list is "An increase in temperature" with a maximal score of 15 points. Signs and symptoms include a body temperature > 38.8 degree Celsius. Following is “Family History” with a possible maximal score of 15. The signs and symptom is consistent with autosomal dominant inheritance. Lastly on the list is the category labored “Other”. The signs and symptoms for this category include a rapid reversal of MH sign with Dantrolene (score = 5) and an elevated resting serum creatine kinase concentration (score = 10) [8].

The MH clinical grading scale is favoured for use as a tool to diagnose the disease. Moreover, its use may augment any research geared towards MH by permitting comparisons amidst distinct groups of patients. In turn, the clinical grading system provides a new and comprehensive clinical case definition for the malignant hyperthermia syndrome. The incidence of MH reactions range from 1:5,000 to 1:50,000 - 100,000 anesthesias. In like manner,

Table 1. Depicts staging for MH based on point system

Clinical finding with maximal points		Signs and symptoms (Manifestations)
Respiratory Acidosis	15 points	End-tidal CO2 > 55 mmHg & PaCO2 > 60 mmHg
Cardiac Involvement	3 points	Unexplained sinus tachycardia, ventricular tachycardia or ventricular fibrillation.
Metabolic Acidosis	10 points	Base deficit > 8 mEq/L & pH < 7.25
Muscle Rigidity	15 points	Generalized rigidity and masseter muscle rigidity.
Muscle Breakdown	15 points	Serum creatine kinase concentration > 20,000/L units, cola-colored urine, excess myoglobin in urine or serum and a plasma [K+] > 6 mEq/L.
Temperature	15 points	Rapid increasing temperature, T > 38.8*C
Family History	15 points	Autosomal dominant inheritance.
Other		Rapid reversal of MH sign with Dantrolene (score = 5) and an elevated resting serum creatine kinase concentration (score = 10).

the prevalence for genetic abnormalities is 1 - 3,000 cases and inherited in the autosomal dominant pattern. Due to the efforts made in understanding the clinical manifestation and pathophysiology of MH, the mortality has dropped from over 80% 30 years ago to less than 5% in present time [9].

A patient may experience MH at first exposure to anaesthesia but in general, it usually takes an average of 3 exposure incidents to anaesthesia before the signs and symptoms present [10]. Moreover, MH is triggered more in males than females at a rate of 2:1. It is found in all ethnic groups evenly and the highest incidence are the younger population with a mean age of 18. It is estimated that more than 1,000 cases of MH in the US each year [7].

4. CONCLUSIONS AND FUTURE RESEARCH

To date, it appears that determination of whether a particular RYR1 mutation may be associated with only the MHS trait or both MHS and CCD involves the following factors: the functional degree of faulty channel-gating at the molecular level; the degree of physiological response of RYR1 mutant proteins to disease precipitating agents; the degree of change in resting concentration of free cytosolic calcium from normal physiological levels and the measurable decrease in sarcoplasmic calcium stores. Recent research seems to suggest that a quantitative lack of functional RyR1 protein generally results in a more severe phenotype than a circumstance of simple RyR1 malfunction [11]. New evidence suggests the possibility of some sort of physiological 'coping mechanism' via epigenetic silencing of various mutant alleles [12]. We believe that the focus of new research will be aimed at elaboration of the functional consequences of individual RYR1 mutations, on the cellular level, in the context of any apparent epigenetic regulation of mutant RYR1 alleles.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Brislin RP, Theroux MC. Core myopathies and malignant hyperthermia susceptibility: A review. Pediatric Anesthesia. 2013;23. Available:http://onlinelibrary.wiley.com.ezproxy.library.dal.ca/store/10.1111/pan.12175/asset/pan12175.pdf?v=1&t=i31qq9vw&s=6c27aab7709d7bdaef6ce153895c1c2a7d70fe11
2. Stratman RC, Flynn JD, Hatton KW. Malignant hyerthermia: A pharmacogenetic disorder. Orthopedics. 2009;32(11). Available:http://www.futuremedicine.com/doi/abs/10.2217/14622416.9.11.1657?url_ver=Z39.88-2003&fr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed
3. Ama T, Bounmythavong S, Blaze J, Weismann M, Marienau MS, Nicholson

WT. Implications of pharmacogenomics for anesthesia providers. ANAA Journal. 2010;78(5).
Available:www.aana.com/aanajournalonline.aspx

4. Genetic Home Reference. CACNA1S Gene. NIH Journal; 2018.
Available:https://ghr.nlm.nih.gov/gene/CACNA1S
5. Zhou H, Jungbluth H, Swery CA, Feng L, Bertini E, Bushby K, Muntoni F. Molecular mechanisms and phenotypic variation in RYR1-related congenital myopathies. Brain. 2007;130.
Available:http://brain.oxfordjournals.org/content/130/8/2024.long
6. Rosenburg H, Nyamkhishig S, Riazi S, Dirksen R. Malignant hyperthermia susceptibility. Anesthesiology. 2006;104: 1353-4.
Available:http://www.ncbi.nlm.nih.gov/books/NBK1146/
7. Girard T, Treves S, Voronkov E, Siegemund M, Urwyler A. Molecular genetic testing for malignant hyperthermia susceptibility. Anesthesiology. 2004;1076-80.
Available:http://www.ncbi.nlm.nih.gov/pubmed/16732128
8. Larach M, Localio A, Allen G, Denborough M, Ellis FR, Gronert G, Ording H. A clinical grading scale to predict malignant hyperthermia susceptibility. Anesthesiology. 1994;80:771-9.
Available:http://www.ncbi.nlm.nih.gov/pubmed/8024130
9. Manning B, Quane KA, Ording H, Urwyler A, Tegazzin V, Lehane M, McCarthy TV. Identification of novel mutations in the Ryanodine-Receptor Gene (RYR1) in malignant hyperthermia: Genotype-phenotype correlation. Am. J. Hum. Genet. 1998;62.
Available:http://www.ncbi.nlm.nih.gov/pubmed/9497245
10. Tammaro A, Bracco A, Santolo C, Esposito M, Di Martino A, Savoia G, Nigro V. Scanning for mutations of the ryanodine receptor gene by denaturing HPLC: Detection of three novel malignant hyperthermia alleles. Clinical Chemistry. 2003;49(5).
Available:http://www.clinchem.org.ezproxy.library.dal.ca/content/49/5/761.full.pdf+html
11. Zhou H, Brockington M, Jungbluth H, Monk D, Stanier P, Sewry CA, Muntoni F. Epigenetic allele silencing unveils recessive RYR1 mutations in core myopathies. The American Journal of Human Genetics. 2006;*79*(5).
Available:http://www.sciencedirect.com.ezproxy.library.dal.ca/science/journal/00029297/79/5
12. Zhou H, Yamaguchi N, Xu L, Wang Y, Sewry C, Jungbluth H, Treves S. Characterization of recessive RYR1 mutations in core myopathies. Human Molecular Genetics. 2007;16(10).
Available:http://hmg.oxfordjournals.org.ezproxy.library.dal.ca/content/16/10/1269.full.pdf+html

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