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SPECIAL ARTICLE

From the *Journal* archives: Hereditary aspects of malignant hyperthermia

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Editors' Note: Classics Revisited

Key Articles from the *Canadian Journal of Anesthesia* Archives: 1954-2013

As part of the *Journal's* 60th anniversary Diamond Jubilee Celebration, a number of seminal articles from the *Journal* archives are highlighted in the *Journal's* 61st printed volume and online at: www.springer.com/12630. This article, the last in our series, was selected on the basis of its novelty at the time of publication, its scientific merit, and its overall importance to clinical practice: *Britt BA, Locher WG, Kalow W.* Hereditary aspects of malignant hyperthermia. Can Anaesth Soc J 1969; 16: 89-98. Drs. Sheila Riazi, Kevin Nolan, and Henry Rosenberg provide expert commentary on this report that significantly contributed to our knowledge of what at the time, was a poorly understood anesthesia-related syndrome that lead to many deaths and much fear regarding this condition brought on by exposure to volatile anesthetic gases and depolarizing muscle relaxants.

Hilary P. Grocott MD, Editor-in-Chief
Donald R. Miller MD, Former Editor-in-Chief

Article summary

Marked hyperthermia, a syndrome often associated with rigidity, respiratory and metabolic acidosis during general anesthesia with halothane, or other potent volatile agents and succinylcholine, is potentially a fatal condition and a difficult clinical problem. During the course of examining 115 such cases, the syndrome was not discerned in infancy or old age, and possible etiologies, such as thyroid storm, sepsis, and pheochromocytoma, were excluded.

Furthermore, the majority of patients were Caucasian, and there were no significant differences among the types of surgeries or gender of affected individuals.

Seeking to determine the inheritance pattern of the syndrome, the authors discussed the inherent difficulties studying the pattern of inheritance in malignant hyperthermia (MH) as it has a variable penetrance (individuals do not show a reaction with every anesthetic, especially with that of shorter durations). In addition, there is a natural elimination of probands due to disease fatality and few progeny.

Referring to at least 43 familial cases out of 115 reported worldwide, the authors examined the hereditary

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nature of the disease. They explored this further by studying a pedigree of 450 individuals extending over eight generations with 21 reactions in 20 individuals, including eight deaths.

The authors concluded that a pattern of autosomal dominant inheritance occurred in three successive generations, with a one-to-one ratio of affected individuals (using both biased and unbiased estimates) and lack of any evidence for recessive or X-linked inheritance.

Furthermore, they found reduced penetrance (transmission from a non-visibly affected parent to their offspring) and variable expressivity (difference in severity of cases), both signalling towards possible modifying factors. They argued against polygenic inheritance based on similar severity between affected parents and affected offspring. In addition, they discussed the sporadic cases (about 50 reported at that time), raising the possibility of *de novo* mutations. Dr. Britt and co-authors also considered the possibility that these anesthesia-related reactions are influenced by factors in the patient's environment or are related to the presence of musculoskeletal disease. Features suggesting myotonia or muscular dystrophy as well as abnormalities such as kyphoscoliosis, hernias, strabismus, and ptosis were considered as possible signs of underlying disease states. Their study of the large pedigree, however, did not support association of MH with any musculoskeletal disorders, and the authors suggested further investigation for this association. It was concluded that there is no evidence for possible mitochondrial involvement in MH.

Authors: *Britt BA, Locher WG, Kalow W*

Citation: Can. Anaesth Soc J 1969; 16: 89-98

Purpose: The purpose of the paper was to review the reported cases of MH to that point in time in order to describe the inheritance of the syndrome in affected families and the likelihood of association with other disorders.

Principal findings: That MH is an inherited disorder in humans was clearly shown by the description of 43 known familial cases, including two large multigenerational families with multiple fatal MH events.

Analysis of the inheritance of the MH clinical syndrome in three successive generations of a large MH family with 20 affected members, including eight fatal anesthetics, allowed exclusion of X-linkage and recessive forms of inheritance and supported an autosomal dominant mode of inheritance. There were sporadic cases – cases with no known affected relatives so the mode of inheritance could not be determined. The analysis also showed evidence of reduced penetrance and variable expressivity of the MH trait.

There was no evidence of increased incidence of musculoskeletal abnormalities, endocrinopathies, or association with specific surgical procedures.

Conclusions: Malignant hyperthermia is an inherited autosomal dominant condition with incomplete penetrance and variable expressivity. Anesthetic records and clinical data indicate MH as monogenic rather than polygenic in nature. The association of MH with musculoskeletal disorders requires further investigation.

This article was written in 1969 by a team[1] that included Dr. Werner Kalow, often described as the "father of pharmacogenetics"; Dr. Beverly Britt, an anesthesiologist devoted to unravelling the biochemical and genetic bases for malignant hyperthermia (MH); and Dr. W.G. (George) Locher, a clinical anesthesiologist practicing in Wausau, Wisconsin. It was the first thorough analysis of all known MH cases ($n = 115$), including a previously published report of one of the first cases of MH with a family history of anesthetic-related deaths.[2] The main conclusion of the earlier work, i.e., that predisposition to MH is a genetic trait, provided a starting point for the research into this mysterious and potentially fatal condition. Dr. Britt's insights and personal efforts to collect and analyze all available clinical data on MH cases put the syndrome "on the medical map" and led to many studies of MH in laboratory and clinical settings. Efforts to determine the specific genetic and biochemical defects underlying MH susceptibility had been hindered by the absence of accurate phenotypic diagnostic criteria. Patients with MH have few signs of problems in the absence of anesthesia, and at the time of publication of their paper, the only method of detecting the trait was the observation of an MH reaction during or following anesthesia. Recognition of the heritable nature of the disorder opened the possibility to the development of a pre-symptomatic test for MH among family members who were likely carriers of the MH trait. Drs. Beverly Britt and Werner Kalow in Canada and Dr. Richard Ellis in the UK developed the first laboratory-based diagnostic tests of MH based on the observation of muscle rigidity during an MH episode. They tested the response of biopsied skeletal muscle to agents, namely, caffeine and halothane, known to release intracellular calcium from muscle stores. They observed that muscle fibres from MH patients responded with stronger contractures as compared with those from patients not susceptible to MH. The standardized caffeine-halothane *in vitro* muscle contracture test introduced in 1980s by the European MH Group (IVCT)[3] and by the North American MH Group (CHCT)[4] has proven useful in determining MH susceptibility and remains the gold standard for diagnosing MH today. Furthermore, accurate assessment of the MH status of members of the families under study led to analysis of genetic linkage in the late 1980s and then direct DNA analysis of large MH families.[5] As a result, the ryanodine receptor gene was identified as a candidate for predisposition to MH, and in 1991, Dr. David MacLennan

of the University of Toronto identified the first MH-causative *RYR1* mutation in humans.[6] Today, MH (MIM #145600)[A] is universally recognized as a subclinical autosomal dominant pharmacogenetic disorder of skeletal muscle caused by defective intracellular calcium homeostasis and presenting with a potentially lethal hypermetabolic reaction to inhalational anesthetics and the depolarizing muscle relaxant, succinylcholine.[7,8] Extensive investigation of the etiology and pathophysiology of MH carried out since the publication of this paper in 1969 has led to a better understanding of the biochemical changes and clinical expression of the syndrome. Thus, genetic studies have proven that mutations in the *RYR1* gene are associated with MHS in over 70% of cases[9] and have justified the introduction of clinical genetic diagnostic testing in selected situations. Although there are over 300 DNA variants in the *RYR1* gene, only about 33 have been definitely proven to be causal for the syndrome. The list of the accepted causal mutations may be found on the website of the European MH Group (EMHG.org). Nevertheless, since about 30% of MH families do not carry *RYR1* mutations or variants, it is likely that other genes or mechanisms play a role in the pathophysiology of MH. Linkage studies in some of those families point to the involvement of alternate chromosomal loci, but thus far, MH-associated mutations have been found only in the *CACNA1S* gene (encoding the alpha subunit of the skeletal muscle voltage-gated calcium channel).[7,9] Genotype-phenotype discordance (i.e., dissimilarities between genetic and CHCT results), observed in a small percentage of MH families, is additionally challenging for genetic research. Further, despite the advances in MH research, causes of reduced penetrance and variable expressivity of MH traits remain to be clarified. It is known that the triggering agents and environmental factors, such as metabolic state and body temperature at the beginning of anesthesia, can influence the clinical characteristics of the MH reaction. It is also possible that variants in genes encoding for proteins involved in excitation-contraction coupling could modulate the response of the muscle to trigger agents. Recent studies have indicated that aberrations of a variety of proteins that regulate intracellular calcium can also, under certain conditions, lead to the biochemical changes predisposing to MH. In addition, the authors discussed sporadic cases as possible non-genetic cases, which, as we understand now, could be either representative of an incomplete penetrance or due to *de novo* mutations.[10] In recent years, it has been shown that certain myopathies predispose patients to MH, including central core disease and nemaline myopathy, Brody myopathy, and a few others. Several recent studies have revealed the relationship between exertional heat illness, exertional rhabdomyolysis and MH.[11,12] Interestingly, in some cases, DNA variants associated with these syndromes are located in the *RYR 1* gene.[13,14] In contrast, mitochondrial myopathies show no apparent relationship with MH, whereas the risk for MH in conditions associated with recessive inheritance of *RYR 1* mutations remains uncertain. In young patients suffering from significant myopathic changes, we suggest a preoperative patient evaluation in conjunction with a neurologist well versed in neuromuscular disorders. Of course, treatment for MH should be instituted when a myopathic patient develops fever, tachycardia, hypercapnia, rhabdomyolysis, and/or hyperkalemia perioperatively.

In summary, this publication in 1969, less than ten years after the first descriptions of MH, provided useful clinical insights into MH and set the stage for a large number of clinical and laboratory-based studies, including genetic studies, aimed at identifying those at risk for MH.

Key points

- When this article was written in the late 1960s, the genetic nature of MH susceptibility was implied by only one previous study,[2] and the pattern of inheritance was still uncertain. Using data from a large family whose health records had been meticulously collected and analyzed by Dr. W.G. Locher, as well as a number of other familial cases, Drs. Kalow and Britt deduced that MH was inherited as an autosomal dominant trait.
- The authors note the strikingly elevated body temperature and muscle rigidity associated with the use of succinylcholine and with halothane or other potent volatile agents and an apparently higher incidence in children and young adults. Importantly, faulty anesthetic practice and endocrine disorders (such as thyroid disease), were found not to be a cause of the signs of MH.
- Furthermore, the MH trait is expressed with reduced penetrance and expressivity, which explains why some patients may not manifest the syndrome on every anesthetic and the varied clinical presentation.
- Confirming the autosomal dominant pattern of MH inheritance set the stage for genetic studies in animals and humans which found that mutations in the *RYR 1* gene encoding the calcium release channel of skeletal muscle underlie up to 70% of MH cases.
- In a small percent of families, MH-associated mutations have been found in the *CACNA1S* gene encoding the alpha subunit of the skeletal muscle voltage-gated calcium channel – a protein that interacts with the ryanodine receptor. Further genetic studies have

[A] The catalogue assignment for a Mendelian trait in the *Mendelian Inheritance in Man* (MIM) system.

identified several other genes potentially responsible for susceptibility to MH.

- The study did not find an association with musculoskeletal abnormalities or with myotonias specifically, although they speculated that there might be an association with mitochondrial disorders. Subsequent research has shown that several congenital myopathies that are also associated with variants in the *RYR1* gene (e.g., central core disease, multiminicore disease, and nemaline myopathy) predispose to MH; however, there does not seem to be a relation between MH and mitochondrial myopathies.

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