

Preoperative diagnosis of malignant hyperthermia

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Did you know: Malignant Hyperthermia is the most common cause of death from general anesthetic in otherwise healthy patients?

(Ball and Johnson, 1993)

Way back in 1929, Ombrédanne described anesthesia-induced post-operative hyperthermia and pallor in children with significant mortality, the so called OMBRÉDANNE'S SYNDROME. But he did not detect familial relationships.²

In 1961, Denborough and Lovell after encountering several unexplained anesthetic deaths, diagnosed a new pharmacogenetic syndrome, MALIGNANT HYPERTHERMIA, characterized by muscle rigidity and hyperpyrexia which they ascribed to a hyper-metabolic state.³

They described a 21 year old Australian with an open tibial fracture who was more anxious about anesthesia than about surgery because 10 of his relatives had died during or after anesthesia. Lovell initially anesthetized him with the then-new agent, halothane, but halted the procedure when signs of MH appeared, and subsequently used a spinal anesthetic.

Other important events in Malignant Hyperthermia (or MH) history is the discovery of dantrolene in 1979 by Harrison⁴, the introduction of molecular genetics by McCarthy in 1989⁵ and the discovery of genetic heterogeneity by Levitt and Olckers in 1997.^{6,7}

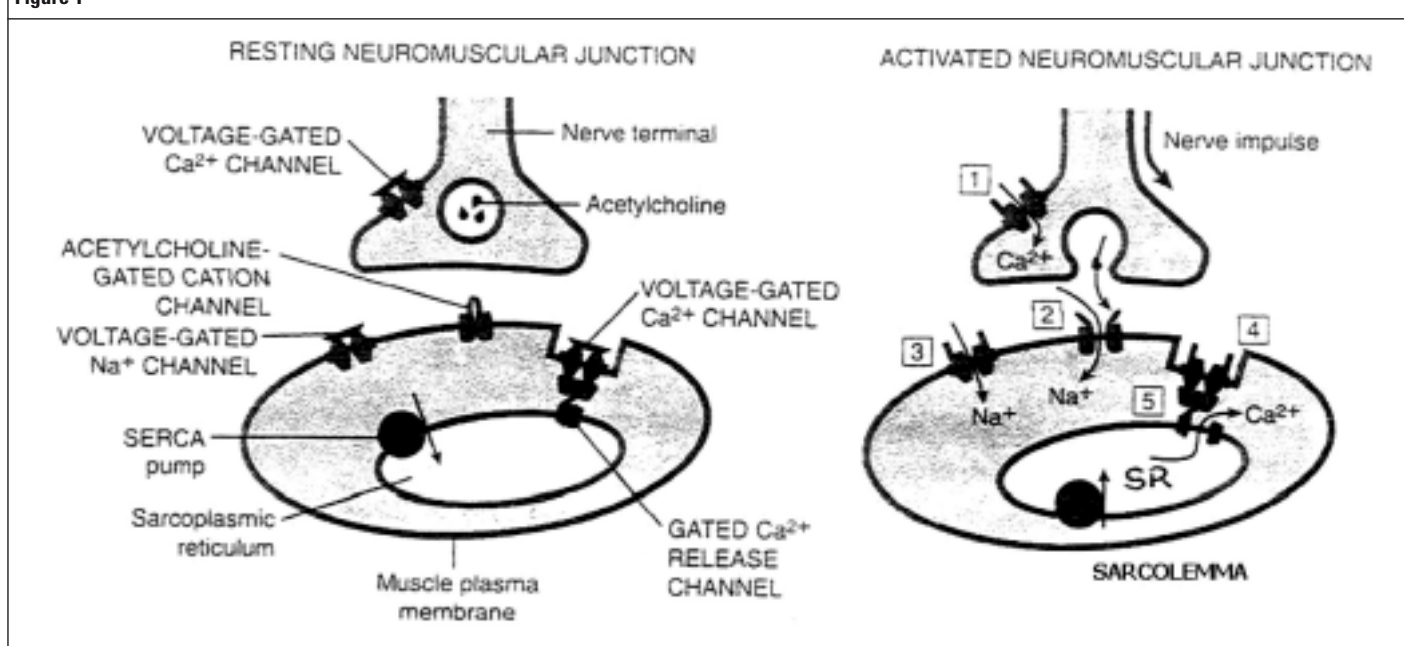
As is now known, MH is an autosomal dominant disorder of skeletal muscle calcium dysregulation.⁸ It is a myopathy, usually subclinical, but after triggering by anesthetic vapours or succinylcholine, an acute loss of intracellular calcium control causes hypermetabolism, rhabdomyolysis, multi-organ failure and death unless immediately treated with dantrolene.⁹ Although it is only anesthetics that can trigger an acute MH reaction they are inconsistent in their ability to trigger. Thus, a MH susceptible patient can trigger on first exposure or only after the fifth or sixth GA unlike the PORCINE STRESS SYNDROME in pigs where any stress such as separation, shipping, weaning, fighting, coitus or preparation for slaughter could lead to an acute MH episode.¹⁰

MH is in essence one of the channelopathies.

Let us look at the key ion channels involved.

Nerve impulses arriving at the nerve terminal activate voltage gated Ca^{2+} channels.¹ The resulting increase in cytoplasmic Ca^{2+} is essential in exocytosis of acetylcholine (Ach). Binding of Ach to postsynaptic nicotinic cholinergic receptors activates this Na^{+} channel causing depolarization of the sarcolemma² and the activation of adjacent Na^{+} channels³, propagate the action potential deep into the muscle via the transverse tubule system. Within the T-tubule system, L-type voltage gated Ca^{2+} channels, the DHPR (Dihydropyridine Receptor), sense membrane depolarization and undergo conformational change.⁴ A physical link be-

Figure 1



tween the α_1 -subunit of the DHPR on the T-tubule and the Ryanodine Receptor on the SR(sarcoplasmic reticulum) is thought to transfer the signal to the SR to release stored Ca^{2+} for muscle contraction⁵, the so-called DIRC (Direct induced release of calcium).¹¹

After SR release of Ca^{2+} , the increased Ca^{2+} removes the tropoin inhibition from the contractile proteins, resulting in actin-myosin-coupling and muscle contraction. The Ca^{2+} pump on the longitudinal tubule of the SR rapidly transfers Ca^{2+} back into the SR, and relaxation occurs when the concentration is restored to less than mechanical threshold. Both contraction and relaxation require ATP, using O_2 and producing CO_2 .

Additional proteins are involved:

- 1) FK 506 = Modulates RyR_1 (Ryanodine receptor) gating
- 2) Calsequestrin = is the major Ca^{2+} binding protein within the SR lumen
- 3) Triadin = couples calsequestrin to the RyR_1
- 4) Calmodulin = regulates RyR_1 channel activity according to cytoplasmic $[Ca^{2+}]$ ¹²

In normal skeletal muscle the muscle contraction is caused by DICR (Direct induced release of calcium) through direct coupling of the α_1 -subunit of DHPR and RyR_1 . But in MH skeletal muscle the muscle contraction is abnormal and continuous through markedly increased intracellular Ca^{2+} caused by CICR (calcium induced release of calcium). Thus the abnormal RyR_1 receptor is not singularly stimulated by the α_1 subunit of DHPR but continuously by the released Ca^{2+} to release more Ca^{2+} : **THUS FIRING A HYPERMETABOLIC STATUS.**¹³

Thus the ryanodine receptor is synonymous with the Ca^{2+} release channel in the SR. It was identified after the purification of a toxic plant alkaloid ryanodine which caused profound muscle rigidity.

There are 3 known isoforms:

- 1) RyR_1 in skeletal muscle, encoded by genes on human chromosome 19q12.1-13.2(5)
- 2) RyR_2 in the heart (1q42.1-q43)
- 3) RyR_3 in the brain (15q14-q15)

So what causes MH?

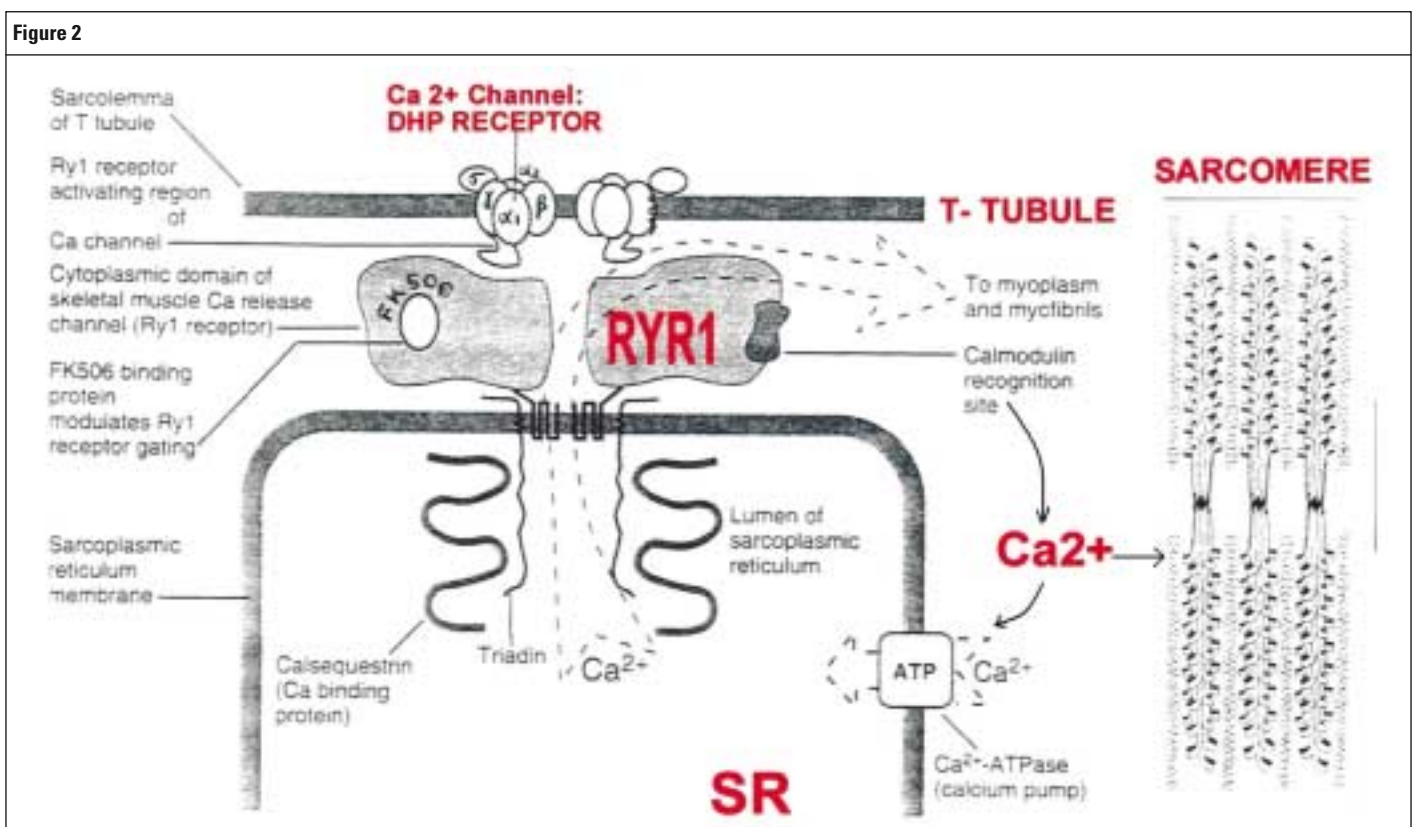
Mutations in RyR_1 on chromosome 19 and DHPR on chromosome 17.¹⁴ The porcine MH model represents a homogenetic mutation namely a substitution of Cys for Arg at position 615 (ARG 615 Cys), but in humans the genetics are heterogeneous,¹⁵ meaning that other loci are also involved in the expression of the clinical trait. Currently, there are 8 Malignant Hyperthermia candidate loci involved: $RyR1$, $CACNA1S$, $CACNA2D1$, $MHS4$, $MHS6$, $LIPE$, $DM1$ and dystrophin.

If we keep in mind that skeletal muscle comprises 40-50% of total body weight we can imagine when MH is triggered, the striking increase in metabolism can result in intense muscle rigidity, tachycardia, fever, hypercarbia, hypoxia, combined respiratory and metabolic acidosis associated with increased permeability of muscle with increased potassium, ionized calcium, CK, myoglobin and serum sodium. As MH progresses disseminated intravascular coagulation, multi-organ failure and death may develop.¹⁶

YES, it is true that dantrolene reduced the mortality from 80% to 8%^{10,17} but MH still remains the most common cause of death from general anesthetic in otherwise healthy patients.

Identification of the MH trait prior to anesthesia is of major therapeutic importance. This step alone can reduce mortality from MH reactions to nearly zero.¹⁸

Although many MH susceptible individuals present clinically totally normal¹⁹ there is a strong and genuine association with congenital musculoskeletal defects to raise our index of suspicion. Strazis and Fox did a huge retrospective meta-analysis in 1993 on 503 MH positive patients between 1965-1992 in 26 countries worldwide and found that 30% **CLINICALLY HAD A MUSCULOSKELETAL DEFECT!**²⁰



1. SKELETAL MUSCLE

a) Clinical:

Muscle bulk and strength are excessive, with the muscle bellies often being rounded rather than fusiform and not always bilaterally symmetrical.

Intervening areas of muscle atrophy are usually so small that they are largely masked by the hypertrophied muscle. In a few patients, however, the atrophied muscle groups are predominant. These individuals may show frank arthrogryposis and an abnormal gait. The muscles, although strong, are sometimes not well coordinated; opposing muscle groups do not seem to be well balanced. The patients, therefore, while active in sports, are generally not very proficient unless the sport is one requiring great physical strength but minimal coordination, for example weight lifting. Because of the lack of motor coordination, some MH children experience difficulty learning to write.

Many, but not all, patients complain of muscle cramps that occur either spontaneously, during an infectious illness, or during or after exercise. When present, these cramps range from mild and infrequent to continuous and incapacitating. It's worse in winter and relieved by warmer climates but recur shortly after the return to cold weather. One must have a high suspicion in patients with a combination of unexplained muscle cramps and a high CK.²¹

Some other variable findings are:^{22,23,24}

- Stocky, short stature
- Joint hypermobility and spontaneous joint dislocations occurring after only minimal trauma
- Ptosis and squint, often both present in the same person
- Thoracic kyphosis in conjunction with lumbar lordosis, and mild scoliosis
- Hernias, usually congenital inguinal hernias, but also umbilical and hiatal hernias
- Various types of clubfoot
- Chronic muscular low backache and herniation of the nucleus pulposus induced by relatively minor trauma
- Pectus carinatum and other sternal deformities
- Hypoplasia and decreased mobility of the mandible
- Poor dental enamel and misplaced teeth
- Winged scapulae
- Undescended testicle
- Calcium stones in ureter or gallbladder
- Dislocated patellae
- Split palate or high arched palate
- Retinal detachment
- Hyperactive personalities are occasionally seen in MH subjects

Bronwell²⁵ described in 1988 various musculoskeletal syndromes associated with MH:

- i. Conditions almost always associated with MH:
 - Central Core Disease (Hypotonia + Weakness)²⁶
- ii. Conditions possibly associated:
 - Duchenne Muscle dystrophy (proximal muscle weakness)²⁷
 - King-Denborough syndrome (Criptorchidism + Pectus Carinatum + Kifoscoliosis + Low placed ears + Webbed neck)
 - Noonan syndrome
 - Myo-adenylate Deaminase Deficiency syndrome
 - Schwart-Jampel syndrome
 - Myotonia congenita
 - Myotonia paramyotonia
 - Hypokalemic familial periodic paralysis
 - Sarcoplasmic reticulum ATPase deficiency syndrome

- Limb girdle muscle dystrophy
- iii. Conditions where association is coincidental:
 - Sudden infant death syndrome
 - Neuroleptic malignant syndrome
 - Glycogen storage diseases
 - Burkett's Lymphoma
 - Osteogenesis Imperfecta

b) Electromyography

Many MH patients show electromyographic changes, but the test is not diagnostic in itself. An increased incidence of polyphasic action potentials and fibrillation potentials occurs.

2. HEART MUSCLE

Number of MH patients have symmetrical cardiac myopathies.²¹

a) Electrocardiograms:

More than one-third of MH patients with positive muscle biopsies have abnormal ECG's. The most commonly observed findings are ventricular or atrial hypertrophy, or both, bundle branch block and myocardial ischemia.

Diagnosis of cardiomyopathy in MH patients is important since paroxysmal arrhythmias have occasionally caused their death.

b) Echocardiograms:

Most heartsonars have been within normal limits. A few, however, have revealed evidence of mitral valve prolapse.

c) Cardiac Catheterization:

Increased LVEDP(left ventricular end-diastolic pressure) , LV dilatation, abnormal contraction patterns and decreased ejection fractions.

Despite this, clearly the preoperative assessment of a patient should include questions relating to previous exposure to anaesthesia and the family anaesthetic history. A family history of an unexplained, unexpected anaesthetic death or cardiac arrest is often significant. NOT ASKING could be a serious medico-legal offence.²⁸

3. LABORATORY

a) Serum CK elevations

The rise of the CK value rather than the absolute value is important. CK's serve also as a prognostic factor in treatment with Dantrolene or where CK value should decrease.

IMPORTANT TO KEEP IN MIND, CONDITIONS THAT GIVE FALSE INCREASED OR DECREASED VALUES:

False low CK values: If the sample is:

- Exposed to light
- Or not promptly frozen in dry ice or liquid nitrogen

False high CK values if:

- patient exercised within a week or two of sampling
- excessive tourniquet pressure
- forcible suction of blood through the needle
- squirting of blood against the wall of the syringe
- recent myocardial infarction
- muscular dystrophy and other myopathies
- paranoid schizophrenia
- various neurological disorders
- hypothyroidism
- acute and chronic alcoholism
- recent IM injection
- recent muscle trauma

b) IVCT and GENETIC TESTING

IMPORTANT PERSPECTIVE: none of the clinical stigmata is in essence diagnostic of MH but should wake some suspicion of MH in your pre-op examination.

Due to a lack of certainty in diagnosing MH on clinical signs outside anaesthesia, an MH in vitro contracture test (IVCT) for biopsied skeletal muscle samples has been developed. These procedures are, however, very invasive and expensive and not routinely done in South Africa at present. Thus, this necessitates the need for a less invasive means of diagnosing MH and therefore genetic screening is the cutting edge of MH research.²⁹

If we look at the epidemiology of MH, we see that the prevalence of MH in the general adult population is 1:40 000 and 1:15 000 in children. And MH occurs in 1:4200 anaesthetics involving potent volatile agents in combination with succinylcholine.³⁰

It is known that MH is much more prevalent in patients with musculo skeletal abnormalities although no prevalence study has been done to quantify MH in musculoskeletal disease. 1:200 is regarded as the estimated prevalence.³¹ Because these patients are much more prone to be exposed to a general anesthetic for surgical correction of their musculoskeletal deformity, it is important to know the prevalence of MH to see if it is sensible to do genetic screening for MH as part of the preoperative management.

Therefore we embarked on a multi-centre international study to determine the prevalence of a positive genotype of MH in patients with musculoskeletal disease like club feet.

Up to now we have only clinical impression and suspicion to work with. After this study we will be able to put numbers to our suspicion!

Since all these musculoskeletal disorders, along with MH, share the common property of having skeletal muscle as the defective end-organ, it is intuitive to speculate that they may indeed share some common disordered mechanism which could allow them to have a significant inter-relationship.

The crux of the matter is that the diagnosis of MH prior to anaesthesia is the best way to avoid an MH reaction during anaesthesia. A high index of suspicion and alertness for the typical stigmata of MH is the most important aspect for the practicing anaesthesiologist in the management of MH.³²

Fortunately MH is rare, but the occurrence of new cases remarkably remains the same. Until such time as there is a routine preoperative blood test for MH susceptibility the mortality and morbidity for an MH crisis will continue to depend solely on the skills of the anaesthetist.

So, chew on this one: before you give the Scoline and Halothane, LOOK FOR MH!!!

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