Malignant hyperthermia

Michael Denborough

A specific inherited muscle membrane disorder predisposes to a variety of clinical problems. The most common is malignant hyperthermia (MH), a dangerous hypermetabolic state after anaesthesia with suxamethonium and/or volatile halogenated anaesthetic agents. MH may also be triggered in susceptible individuals by severe exercise in hot conditions, infections, neuroleptic drugs, and overheating in infants. Inbred pigs have provided a helpful model, and experiments on these animals and in MH-susceptible patients have shown that the essential biochemical abnormality is an increase in calcium ions in the muscle cells. This knowledge has led to a specific muscle test to identify susceptibility to MH and to a specific treatment, dantrolene; and as a result the case-fatality rate in MH has fallen from 70% in the 1970s to 5% today. In pigs susceptibility to MH is caused by a single mutation in the ryanodine receptor (RYR) in skeletal muscle. In man the genetics is more complex and three clinical myopathies that predispose to MH have been defined. By far the most common is inherited as a mendelian dominant characteristic and at present mutations in the human RYR account for no more than 20% of susceptible families.

The story of malignant hyperthermia (hyperpyrexia, MH) begins on April 14, 1960, when a 21-year-old student was run over by a car and sustained compound fractures of his right tibia and fibula. In the casualty department of the Royal Melbourne Hospital, Australia, he was less concerned about his leg than by the prospect of a general anaesthetic; he said that 10 close relatives had died during or after anaesthesia, usually for minor procedures. Because ether had been incriminated in all the previous cases, it was decided to proceed cautiously with halothane, which had recently become available. Unfortunately after 10 min of anaesthesia the patient became acutely ill; his blood pressure was falling, pulse rate rising, and he was cyanosed and felt very hot. The soda-lime canister was also hot, and it was changed. The anaesthetic was stopped and the patient was rubbed down with ice-cold packs. He recovered and his subsequent course was uneventful. Detailed clinical examination and routine pathological and biochemical tests revealed no abnormality but inquiry into the deaths in the family indicated a previously undescribed inborn error of metabolism inherited as a dominant characteristic. In the hope that others might have noted similar clinical events, this patient’s anaesthetic complication was described in *The Lancet*, but with no response.

A year later the man needed another anaesthetic, this time for a stone impacted in his left ureter. Although considerable discussion the patient was connected to every possible monitor and given a spinal anaesthetic, which he tolerated uneventfully. The knowledge that local anaesthesia could be used safely was a great help because the patient came from a very large family, one very prone to accidents and operations. 2 years later I learned of three anaesthetic deaths in a family in Wisconsin, USA, and further cases were published. One such child had died in Toronto, Canada, which led to 13 cases of MH being presented at a symposium in Toronto in 1966. One interesting observation to come out of this meeting was that during the MH reaction some patients developed muscular rigidity. The syndrome became known as malignant hyperthermia or MH—hyperthermia, because a steep and rapid rise in body temperature was a common accompaniment, and malignant, because in those days the case-fatality rate was 70%.

In November, 1969, there was a second case of MH at the Royal Melbourne Hospital. A 51-year-old man with no family history of anaesthetic problems and who had had uneventful anaesthesia with ether for an appendicectomy when he was 21, had sustained a compound fracture of the right leg in a motor accident. He was given succinylcholine and halothane, became acutely ill, and died, 24 h after the anaesthesia had been induced. 3 h after the reaction had started it was noted that his right arm was rigid, and because muscle rigidity had been noted in some patients with MH, his serum creatine kinase (CK) activity was measured. His serum CK rose from 280 IU/L at 3 h to 20 500 IU/L at 24 h, just before he died. Clearly, the anaesthetic drugs had induced severe rhabdomyolysis in a susceptible individual, and the implication was that individuals who are susceptible to MH have an underlying muscle disease.

The propositus in the original family was contacted and his serum CK was found to be very high. His father, a paternal aunt, and his sister had raised serum CK too high, though his brother’s CK was normal. His father and paternal aunt had clear evidence of a clinical myopathy.

Meanwhile Isaacs and Barlow in Johannesburg, South Africa, independently observed that some relatives of MH patients had high serum CK activities. They found that dog muscle contracted on exposure to chloroform, and because of this decided to study caffeine-induced contraction in human muscle. This led to the important observation that caffeine contracture is augmented in patients who are susceptible to MH, and this was shown by Ellis and colleagues to apply to halothane also.


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**Myopathy and MH**

Everyone who is susceptible to MH has an underlying disorder of the muscle-cell membrane, and three clinical myopathies that predispose to MH have been defined. Although other myopathies have been mentioned in association with MH, these three are the only ones in which the predisposition to MH has been established.

**Evans myopathy**

By far the most common myopathy predisposing to MH is usually referred to as the MH myopathy, and is inherited as a mendelian dominant. It is usually subclinical, but some muscle wasting may occur, often in the lower thigh. The serum CK may be raised, but it is often normal. The myostructural changes underlying this myopathy have been studied in detail, but they are non-specific and variable, both in type and severity. To distinguish this myopathy from the other two associated with MH, we refer to it as the Evans myopathy, after the family in which MH was first described.

**King-Denborough syndrome**

This myopathy was identified in a nationwide survey of MH in Australia and New Zealand in 1970. It is rare though several other examples have been described. It is found in children, usually boys. The boys are usually small for their age and have undescended testes, lumbar lordosis, thoracic kyphosis, and pectus carinatum. The children also have an unusual facial expression with a small chin, low-set ears, ptosis, and antimongoloid obliquity of the palpebral fissures. The myopathy is probably inherited as a recessive trait.

**Central core disease**

An association between MH and central-core disease was recognised in 1973, and all members of the families in which central-core disease has been diagnosed should be regarded as susceptible to MH until proved otherwise. Histochemical and electronmicroscopic examination of muscle in affected individuals shows striking non-staining lesions extending along type I fibres, and there is often type I atrophy. However, some individuals in central-core families, who are shown by pharmacological tests to be susceptible to MH, may have normal muscle histology. This suggests that the cores are a late degenerative change.

**Clinical presentation: anaesthetic complications**

The commonest clinical presentation of MH is a hypermetabolic state in a genetically susceptible individual in response to certain anaesthetic agents, notably suxamethonium or halogenated volatile anaesthetics. One of the earliest clinical signs is masseter spasm after succinylcholine. In-vitro muscle testing in patients who have developed this sign alone reveals that 28–50% are susceptible to MH.

In the full-blown syndrome there is a rapid and sustained rise in body temperature, without shivering, either in the operating theatre or in the recovery room, in the absence of any obvious cause such as infection or a hot and humid environment. Tachycardia, cyanosis, generalised muscle rigidity, and cardiac arrhythmias are common clinical signs. There may be heating and rapid exhaustion of the soda-lime canisters. Acidosis is an early finding and there may also be hyperkalaemia, hyperphosphataemia, and hypocalcaemia from muscle-cell breakdown.

MH is of interest not only to anaesthetists but also to other specialists, such as neurologists, intensivists, renal physicians, and specialists in tropical medicine. This is because the MH myopathy has varied clinical presentations, including heatstroke, gross rhabdomyolysis after a variety of triggers, a chronically raised serum CK, muscle pain, neuroleptic malignant syndrome (NMS), and sudden infant death (SID).

In less obvious cases, MH may be present with one or any combination of the above clinical signs. The first indication of MH may be an unexplained cardiac arrest or cardiac arrhythmia. A rise in end-tidal CO₂ is often the earliest indication of MH, and now that this is widely measured in clinical anaesthesia MH may be picked up before the more florid signs develop. Previously apparently uncomplicated anaesthesia with halothane and/or succinylcholine does not exclude the diagnosis of MH on a subsequent occasion. Factors such as the concentration of the anaesthetic drugs used, the duration of the anaesthesia, and the degree of MH susceptibility of the patient may explain why one anaesthetic procedure is uneventful while another in the same patient is not.

When MH was first recognised as a complication of anaesthesia the case-fatality rate was 70%. Today, with the use of a specific drug for MH and the introduction of an in-vitro muscle-contracture test (see below) to identify susceptibility to MH in individuals and their relatives, the case-fatality rate is only 5%.

**Clinical presentation: non-anaesthetic presentations of MH**

MH myopathy
Vigorous exercise in hot conditions may precipitate MH in susceptible individuals. The basis of this presentation has been explained by phosphorus-31 nuclear magnetic resonance spectroscopy, which has shown that not only do halothane and caffeine induce greatly increased metabolism in MH-susceptible muscle in vitro but also anoxia and ischaemia produce similar increased metabolism in MH-susceptible muscle in vitro and in vivo.16

The association between MH and heatstroke was first recognised in 1980, when a 19-year-old soldier (A) developed heatstroke during a route march.17 He was unconscious and unresponsive to painful stimuli, with a rectal temperature of 42°C. He had metabolic acidosis, disseminated intravascular coagulation, and was bleeding from the bowel. He was given intravenous dantrolene and improved within an hour. His rectal temperature did not rise above 39°C for 11 days. The symptoms worsened during the following week and improved at weekends. Serum CK activity was 1056 IU/L on one Saturday and 544 IU/L on the following Monday. Physical examination showed no abnormalities. Because of the structural similarity between the gas and halothane, its effect on muscle contracture was studied in vitro and found to be identical to that of halothane. The patient changed his job, and his symptoms completely in a few days. In-vitro muscle testing in the son showed that he was susceptible to MH.

The only significant finding in infection screening was a four-fold rise in the antibody titre to influenza B virus. His father had died from a similar illness at age 33 and his son (F) had a similar illness at the same time and also had rhabdomyolysis (CK 3550 IU/L), but recovered completely in a few days. In-vitro muscle testing showed that he was susceptible to MH.

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The findings in these five patients have been confirmed by a large study in 55 patients with heatstroke in Marseille, France. Six of these patients were MH susceptible on in-vitro testing and 13 others gave an increased response to halothane or caffeine. Relatives of some of these patients were also MH susceptible.

Rhabdomyolysis
A 32-year-old man developed an influenza-like illness in 1989 with headache, fever, vomiting, and muscle aches. He had severe rhabdomyolysis (serum CK 243 000 IU/L) and died in intensive care 1 week after his illness began. The only significant finding in infection screening was a four-fold rise in the antibody titre to influenza B virus. His father and one of his sisters were subsequently shown to be susceptible to MH.

A 23-year-old professional athlete (E) developed rhabdomyolysis and mild renal failure after training for the 200 m sprint. He had had a similar episode of mild renal failure and rhabdomyolysis 2 years previously after hard physical exercise as a labourer. In-vitro muscle testing revealed susceptibility to MH.

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All the patients had abnormal serum CK activity (figure 1) and unequivocal positive contracture tests (figure 2).

Figure 2: Muscle contracture test results in illustrative cases of non-anaesthetic presentations of MH

A 36-year-old man (B) developed troublesome muscle pains after playing squash and drinking moderate amounts of alcohol. His serum CK was consistently raised and in-vitro muscle testing showed that he was susceptible to MH; his father and one of his sisters were subsequently found to be susceptible also.

Over 3 years a 22-year-old soldier (C) experienced about 20 attacks of headache, lightheadedness, nausea, chest pain, and fatigue after exertion. He also had aching legs below the knee which were thought to be shin splints. The symptoms were associated with exercise in hot conditions, such as 3–4 km runs or aerobic exercise, and he would feel unwell for 2–3 days. After one episode his serum CK was 18 600 IU/L on the fourth day after exercise. Cardiological testing was normal. In-vitro muscle testing revealed susceptibility to MH, and his father was also shown to be susceptible to MH.

A 19-year-old soldier (D) had heatstroke during a combat exercise. A punch biopsy was normal but his serum CK was persistently abnormal. Muscle testing 5 months later showed that he was susceptible to MH.

A 45-year-old father (H) of a 12-year-old girl who had survived an episode of MH was found to have a serum CK of 650 IU/L and he too was susceptible to MH. While working in his task was to discharge bromochlorodifluoromethane from fire extinguishers before filling them. This work was done in the open air but it was hard to avoid inhaling some of the gas. He complained of malaise and stiffness and weakness in his forearms and hands during the 18 months which he had been in the job. The symptoms worsened during the week and improved at weekends. Serum CK activity was 1056 IU/L on one Saturday and 544 IU/L on the following Monday. Physical examination showed no abnormalities. Because of the structural similarity between the gas and halothane, its effect on muscle contracture was studied in vitro and found to be identical to that of halothane. The patient changed his job, and his symptoms immediately improved. It seems as though this MH-susceptible patient had recurrent rhabdomyolysis from exposure to a halothane-like gas.

Muscle pains
A 65-year-old man (J) had pain in his legs on exertion.

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The leg pulses were normal, as was the rest of the clinical examination. A microtubular myopathy was suspected. Pharmacological testing of biopsy muscle showed that he was susceptible to MH. His 21-year-old son, who had Sturge-Weber syndrome, was subsequently found to be susceptible to MH also.

**Neuroleptic malignant syndrome (NMS)**

NMS has been recognised for over 20 years, and may present clinically in much the same way as MH. A 31-year-old man (K) given fluphenazine by mouth and intramuscularly for 9 months for chronic schizophrenia became nauseated and drowsy, with a fever (38·5°C) and a grand-mal seizure. His CK was 53 000 IU/L. His urine contained myoglobin. The fluphenazine was stopped. 2 months later, when he was fully recovered from his episode and his serum CK was normal (87 IU/L), in-vitro testing showed that he was susceptible to MH. His brother was also susceptible.

Others have found MH susceptibility in contracture tests in patients who have recovered from NMS and several patients with NMS have been successfully treated with dantrolene. Biopsies on six patients who had recovered from NMS gave a caffeine contracture to 1 mmol/L caffeine of 0·4 g in one patient; the others gave negative results. These biopsies were done soon after the patients had experienced severe rhabdomyolysis and 48 h after the dantrolene infusion had been stopped. These two factors may have interfered with the in-vitro tests. We wait for 2 months after a patient has had an episode of acute rhabdomyolysis before testing for MH susceptibility.

Laboratory studies showed that, just as halothane raises myoplasmic Ca²⁺ levels to cause the symptoms and signs of MH, so neuroleptic drugs also raise myoplasmic levels of Ca²⁺, by inhibiting Ca²⁺-dependent ATPase and ATP-dependent Ca²⁺ uptake by the sarcoplasmic reticulum, and accelerating the efflux of Ca²⁺ from the sarcoplasmic reticulum. These laboratory studies provide a clear-cut biochemical explanation for why neuroleptic drugs may trigger MH in susceptible individuals.

**Sudden infant death syndrome (SIDS)**

A 28-year-old man (L) whose son had recently died from SIDS said that 10 years previously he had had three cardiac arrests during an appendicectomy. In-vitro testing showed that he was susceptible to MH. Subsequently biopsies on 15 other parents of SIDS infants showed five MH susceptible, and this is much more common than could have happened by chance. The association between MH and SIDS has also been found in one Danish and two Swedish families, and a significant excess of anaesthetic deaths in SIDS families was also found in an epidemiological study in the USA. MH has also been implicated in the sudden deaths of two teenage brothers whose father was susceptible to MH.

Since that series of five SIDS parents another typical case of MH susceptibility in a SIDS parent has been recognised. This was a 30-year-old nurse (M) who had two normal daughters and then two SIDS sons. His CK was 1300 IU/L. His 3% halothane contracture was 2·6 g and his 2 mmol/L caffeine contracture was 1·15 g. He recalled that his sister had died aged 2 years from an operation for a patent ductus. The reports obtained about this death were strongly suggestive of MH.

There is no indication for routine testing of parents of SIDS children; they have enough to contend with. In one study in which 14 parents of SIDS children were tested, all had negative results. Among 106 pairs of SIDS parents in the same study three gave a history suggestive of MH: a maternal uncle was “packed in ice” after appendicectomy, a mother described postoperative stiffness for 24 h after the removal of a benign papilloma, and a father experienced a raised postoperative temperature on several occasions. It would also be of interest to know the causes in six unspecified perinatal deaths in the 151 families studied, and CK estimations with a view to in-vitro muscle testing would have been of interest in these parents.

**Animal model**

Certain inbred strains of pig are susceptible to MH. In 1966 three pigs being used in experiments on aortic atheroma were given succinylcholine and developed convulsions and died. Soon afterwards pigs being used for liver transplantation experiments developed a fever and convulsions and died in response to halothane.

Pigs that are susceptible to MH have an underlying muscle disease closely resembling the muscle disorder that predisposes to MH in man. Malignant hyperpyrexia has also been described in dogs, cats, and horses. Triggering of MH in susceptible pigs led to the definition of the early biochemical changes that occur in MH. The first major chemical change is the production of lactic acid, accompanied by a drop in blood pH. These chemical changes precede the rise in temperature. The production of lactic acid is accompanied by a rapid rise in blood CO₂ and a fall in bicarbonate. All these changes are due to a rise in Ca²⁺ concentration in the myoplasm, which also accounts for the muscular rigidity and the rise in body temperature. P nuclear magnetic resonance studies in muscle of MH-susceptible pigs showed that the fever in MH is due to the continued Ca²⁺-induced synthesis and hydrolysis of ATP.

MH can be triggered in anaesthetised MH-susceptible pigs not only by anaesthetic agents but also simply by heating. This observation prompted a simple animal experiment to explore a possible association between MH and SIDS. A standard heat challenge in neonatal incubators was applied to eight MH-susceptible piglets and eight matched controls. All eight susceptible piglets developed MH (and seven died); the challenge was well tolerated by the controls. Since the biochemical basis of MH in man and pig is a rise in Ca²⁺ in the myoplasm, these results support the view that the myopathy which predisposes to MH also predisposes to SIDS. The link between them is overheating, a prominent feature of MH and one which is increasingly recognised as an important cause of SIDS.

**In-vitro muscle testing**

The strength of a skeletal muscle contracture is a function of free Ca²⁺ in the myoplasm, and the demonstration of increased contractility in MH-susceptible muscle in response to halothane and caffeine supports a primary biochemical role for raised myoplasmic Ca²⁺ in the development of MH. Halothane raises myoplasmic Ca²⁺ by a direct effect on the muscle-cell membrane, whereas succinylcholine does so by causing muscle fasciculations. Increased contractility to halothane and to caffeine in vitro provides a specific test to identify susceptibility to MH.
Susceptibility to MH can only be identified unequivocally by an in-vitro muscle test. Fascicles of muscle obtained from the thigh by biopsy are exposed to halothane and separately to increasing concentrations of caffeine in vitro. The muscle contractures are increased in patients who are susceptible to MH. This test is now widely used to identify susceptibility to MH in individuals who have had a reaction to inhaled halogenated anaesthetics and/or suxamethonium which is suggestive of MH. If the test in the propositus is positive, it can be offered to first-degree relatives for genetic counselling. In our laboratory a single dose of 3% halothane up to 2% and incremental doses of caffeine. In the USA and in our laboratory a single dose of 3% halothane and incremental doses of caffeine are used. The two protocols give essentially the same results. Occasionally there is a discrepancy between the halothane and the caffeine contractures. The Europeans refer to such results as “equivocal”; US workers and we classify them as “susceptible”. To avoid confusion, none of the illustrative cases in this paper had “equivocal” results, and measurements of contractures to halothane and to caffeine are included for all. If everyone adopted this approach there might be less controversy about possible associations between MH and other muscle diseases or non-anæsthetic clinical presentations.

**Genetics**

The inherited abnormalities in MH-susceptible muscle lie in the regulation of myoplasmic Ca²⁺. The sarcoplasmic reticulum is the main store for intracellular Ca²⁺ in skeletal muscle, and Ca²⁺ is released by excitation-contraction coupling (E-C coupling), which is controlled by at least three specialised structural proteins located in the transverse tubule (T-tubule), in the sarcoplasmic reticulum membranes, and in incompletely defined, triadic elements. Malignant hyperpyrexia is triggered by a rapid, sustained rise in myoplasmic Ca²⁺.

Ryanodine, a plant alkaloid that effects Ca²⁺ release from the sarcoplasmic reticulum, binds to a skeletal muscle calcium release channel, the ryanodine receptor (RYR). This receptor has both a structural and a functional role in E-C coupling. Mutations in the gene for RYR were the first to be considered as candidates for causing MH—indeed an abnormality in skeletal muscle RYR causes MH in pigs. This abnormality is a single mutation in the cDNA sequence encoding the RYR which results in a substitution of Cys for Arg at position 615. It is now possible to differentiate accurately between normal, heterozygote, and MH porcine genotypes.

In human MH the genetics is more complex. Although linkage of MH in some families to the analogous chromosome has been demonstrated this defect is present in less than 5% of MH-affected pedigrees, and mutations in RYR1 (the gene encoding human skeletal muscle RYR) account for fewer than 20% of MH cases studied. A link between RYR1 and central core disease has also been demonstrated.

Chromosomal localisations associated with MH are shown in the panel.

**Treatment**

Dantrolene sodium was synthesised as a possible antibiotic. It was found to induce flaccidity of muscle when injected into mice and this remarkable effect was found to be due to inhibition of E-C coupling in skeletal muscle without affecting neuromuscular transmission or the electrical properties of muscle. This drug, in

### Chromosomal localisations harbouring potentially causative MH-susceptibility loci

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**Chromatic localisations associated with MH-susceptibility loci**

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<tr>
<td>1q32</td>
<td>DHPR-γ subunit?</td>
<td>Unidentified</td>
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<tr>
<td>6q21-22</td>
<td>DHPR-α2/8-subunits?</td>
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| 1q32                      | DHPR-α1 subunit        | Arg1066His⁻¹ |}

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circuiting concentrations that can readily be achieved clinically, causes complete, immediate, and sustained relaxation of caffeine and halothane contractures in vitro in MH-susceptible muscle and is very effective in the treatment of human and porcine MH.

I thank Nichole Taske for advice about the genetics of MH and for preparation of the panel.

References


7 Kalow W, Britt BA, Terreau MH, Haist C. Metabolic error of muscle in MH-susceptible muscle and is very effective in the preparation of the panel.

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