

Malignant hyperthermia

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First described in 1960, malignant hyperthermia (MH) is an inherited disorder of skeletal muscle that can be pharmacologically triggered to produce a potentially fatal combination of hypermetabolism, muscle rigidity and muscle breakdown. Primarily, it is a disorder of concern to anaesthetists as the only universally accepted pharmacological triggering agents are potent inhalational anaesthetics and succinylcholine. For the purposes of family counselling and screening, it is important to distinguish MH from other myopathies that can produce a similar clinical picture during anaesthesia. Confirmation of the clinically suspected MH reaction is by pharmacological *in vitro* contracture tests and histological examination of excised muscle samples. However, DNA diagnosis has recently taken on a limited role (see later).

Epidemiology

There is a wide range of estimates of the prevalence of MH susceptibility in the literature. Similarly, the incidence of reported MH reactions varies from approximately 1 in 40,000 to 1 in 100,000 anaesthetics. Variability in the reported incidence is a result of a combination of a lack of information concerning the total number of anaesthetics given nationally and the inclusion of unconfirmed cases of MH. Extrapolation of these data to estimate the prevalence of the genetic disorder is further complicated by an apparent reduction in tendency to suffer a reaction with increasing age, a preponderance of male reactors and the consistent finding that, on average, patients found to be susceptible to MH have had three previous uneventful general anaesthetics. Most recent estimates of the population prevalence of the genetic susceptibility are between 1:5000 and 1:10,000.

The referral pattern to the Leeds MH investigation unit, which is the UK national centre, has been remarkably consistent for the past 10 years. Around 100–200 new cases are referred annually. In approximately 50% of these referrals, it is not possible to exclude MH on the basis of the clinical history. These patients are screened for MH susceptibility and 40–50% of these are confirmed as new cases of MH. The mortality from MH reactions over the past 10 years is approximately 2–3%.

Clinical features

The primary features of MH are a direct consequence of loss of skeletal muscle cell calcium homeostasis with a resulting increased intracellular calcium ion concentration. In muscle, calcium is the most important second messenger. Persistently elevated intracellular calcium ion concentration causes:

1. Muscle rigidity due to continuous actin–myosin interaction.
2. Hypermetabolism due to: (i) direct stimulation of glycolytic enzymes by the calcium-calmodulin complex; and (ii) indirectly, through the demand for ATP which is required both to fuel the excessive myofilament interaction and to provide the energy source for various membrane calcium pumps that will be operating maximally in order to try and restore calcium homeostasis.
3. Rhabdomyolysis occurs as a result of excessive contractile activity and increased turnover of membrane phospholipids due to calcium activation of phospholipases.

A MH reaction is potentially life threatening because skeletal muscle constitutes 40%

Key points

Successful treatment of a malignant hyperthermia (MH) reaction depends on early diagnosis.

Excessive muscle rigidity following succinylcholine is an indication for investigation of MH susceptibility.

Increasing end-tidal CO₂ concentration and heart rate occur before a rise in body temperature during a MH reaction.

Guidelines for the management of a suspected MH reaction should be displayed prominently in all locations where general anaesthesia is administered.

All cases of suspected MH should be referred for specialist investigation.

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of body mass. Excessive heat results from excessive muscle contraction and from metabolic stimulation. Heat production can so exceed heat-losing capabilities that the body temperature may rise at a rate $> 1^{\circ}\text{C}$ per 10 min. Oxygen delivery is often incapable of meeting the metabolic demands of the stimulated muscle. There may well be arterial oxygen desaturation. Acidosis results from excessive production of CO_2 and lactic acid.

Rhabdomyolysis leads to leakage of potassium ions and myoglobin into the blood. The resulting hyperkalaemia often leads to arrhythmias which may be fatal. Plasma myoglobin concentrations are sufficient to cause renal tubular damage and acute renal failure. Disseminated intravascular coagulation may occur as a result of the release of tissue clotting activators from the necrosing muscle and through the action of the excessive heat.

Clinical presentations

Clinical presentation of MH can be discussed under three main headings: (i) muscle rigidity after succinylcholine; (ii) classical MH; and (iii) other presentations.

Muscle rigidity after succinylcholine

The earliest indication the anaesthetist may have that a patient is susceptible to MH is the observation of excessive muscle rigidity (often restricted to the masseter muscles) after the administration of succinylcholine. It has been carefully documented that, prior to the onset of paralysis, succinylcholine induces masseter muscle spasm (MMS) in most people. In patients susceptible to MH, this response is more likely to be extreme. Extreme MMS can be defined in terms of the intensity and duration of jaw rigidity. For the anaesthetist experienced in the use of succinylcholine, it is that which falls outside previous experience. For the less experienced anaesthetist, the inability to open the patient's mouth 2 min after the administration of succinylcholine, or easily demonstrable resistance to mouth opening 4 min after administration, should be a cause for concern. Approximately 25% of patients referred for testing following an episode of jaw rigidity as the sole feature prove to be susceptible to MH, even when anaesthesia has continued with volatile agents apparently uneventfully. Additional features that increase the likelihood of underlying MH are signs of metabolic stimulation and grossly elevated plasma creatine kinase (CK) and myoglobin concentrations. There may also be evidence of myoglobinuria; this occurs earlier than CK increases. CK reaches a peak approximately 24

h after the insult and, even in patients with no muscle disorder, can reach 50 times the upper limit of normal.

Jaw rigidity and muscle damage resulting from succinylcholine is more marked after inhalation induction with a volatile anaesthetic than following intravenous anaesthetic induction. This is true for patients with and without underlying MH susceptibility. Generalised muscle rigidity following the administration of succinylcholine should never be considered to be normal and is indicative of MH susceptibility or another muscle disorder.

Classical malignant hyperthermia

An untreated classical MH reaction presents with metabolic features, evidence of muscle breakdown and, eventually, muscle rigidity. However, it is clearly inappropriate to allow a diagnosed reaction to progress to the full syndrome, as morbidity and the likelihood of mortality is reduced by prompt intervention. Careful documentation of confirmed cases of MH demonstrate a consistent pattern of development of the various features.

Apart from MMS, the early signs of an impending MH reaction are those of metabolic stimulation. The two most important features are an unexplained increasing CO_2 production and tachycardia. A rise in CO_2 production will be apparent initially as tachypnoea in the spontaneously breathing patient or a rise in end-tidal CO_2 concentration in a patient whose lungs are mechanically ventilated. At this stage, the blood pressure may be unstable (not as consistent or severe as in the porcine model of MH) and there is a tendency for SaO_2 to decline. Rise in body temperature is a later sign, becoming apparent after the increase in CO_2 production and tachycardia. The development of generalised muscle rigidity, raised plasma CK and myoglobinuria are later and more sinister developments. It is at this stage that hyperkalaemia, cardiac arrhythmias and disseminated intravascular coagulation are likely to develop.

Although the sequence of events is quite consistent, the interval between first administration of triggering drugs and the onset of symptoms is variable, as is the rate at which the different features develop. The most rapidly developing reactions have occurred when anaesthesia is maintained with a volatile anaesthetic after succinylcholine has been used to aid tracheal intubation. While it is likely that halothane is the most potent MH trigger of the volatile anaesthetics, the difference in potencies is probably not sufficient to be clinically important. Rapidly developing cases have occurred with each of

Table 1 Differential diagnoses of malignant hyperthermia

Inadequate anaesthesia/analgesia
Inappropriate breathing circuit/fresh gas flow/ventilation
Infection/sepsis
Tourniquet ischaemia
Phaeochromocytoma
Thyroid storm
Cerebral ischaemia
Anaphylaxis
Other muscle diseases

the volatile anaesthetics, as have cases of more insidious onset and gradual development. Other factors influencing the nature of a MH reaction may include other anaesthetic drugs, base-line body temperature, concentrations of circulating catecholamines and the precise nature of the underlying genetic defect. Also, the method of administration of the triggering volatile anaesthetic is probably important. It seems likely that triggering is dependent on a threshold concentration of drug developing at the triggering site in the muscle. Thus, low concentrations of volatile agents used to prevent awareness during artificial ventilation may give rise to a more insidious onset than the higher concentrations used in spontaneous respiration.

Features of a MH reaction will always be present before the discontinuation of the trigger because of the threshold concentration requirement. They will not start after the trigger is removed. The consistency of the relationship between the onset of increased CO₂ production, tachycardia and increased temperature is important. It determines that the observation of a postoperative pyrexia is not indicative of MH if there was no evidence of increased CO₂ production or tachycardia during surgery or in the immediate postoperative period. Confidence in dismissing postoperative pyrexia as being due to MH is entirely dependent on the adequacy of anaesthetic and recovery room records.

The differential diagnoses of a MH reaction is shown in Table 1.

Other presentations

An occasional presenting feature of MH, particularly in the past, has been unexplained, unexpected cardiac arrest or death. It is likely in these cases that the cardinal features of MH were present but not observed, or their significance ignored. With current monitoring standards, it is difficult to envisage this type of presentation.

Another rare presentation is the development of myoglobinuria which may cause acute renal failure in the postoperative

period. This is due to major rhabdomyolysis following the use of succinylcholine. The contemporaneous anaesthetic records of these cases are often not sufficiently detailed to determine whether MH could have been suspected during the operation. It is feasible that severe rhabdomyolysis can occur in isolation.

Management

The key to successful management of MH is its early diagnosis. On recognition of a reaction, several modes of treatment must be instigated simultaneously. The urgency of the situation cannot be over emphasised.

Administration of volatile anaesthetics should be discontinued and the patient's lungs hyperventilated using 100% oxygen with fresh gas flows and type of breathing circuit optimised to eliminate the anaesthetic from the body. Anaesthesia should be maintained with intravenous drugs while surgery is concluded as rapidly as possible. Active cooling measures should be commenced; these include infusion of cold intravenous solutions, application of ice to the axillae and groins and a cooling mattress. Excess blankets and drapes should be removed. Care must be taken to avoid peripheral vasoconstriction that will result from over zealous application of ice to the skin, so preventing heat loss. In extreme cases, and where appropriate technology is available, cooling can be rapidly effected by heat exchange, either through dialysis or by the heat exchanger of a cardiopulmonary bypass machine.

At the onset of treatment, one member of staff must be assigned to the preparation of dantrolene sodium for infusion. Dantrolene is the only drug effective in limiting the accumulation of calcium ions within muscle cells. It does this by acting at the interface between the t-tubular system and sarcoplasmic reticulum. The bottle contains dantrolene 20 mg and mannitol 3 g. The latter is required to solubilise the dantrolene. Repeated doses of dantrolene (20 mg in adults, 1 mg kg⁻¹ in children < 20 kg) should be administered intravenously as soon as possible until the tachycardia, rise in CO₂ production and pyrexia start to subside. Up to 10 mg kg⁻¹ may be required. The average dose is about 3 mg kg⁻¹. If given in time, dantrolene can be dramatically effective. Further doses of dantrolene may be required during the next 48 h if the reaction recurs. However, this is unusual.

Acidosis and hyperkalaemia should be anticipated and treated using bicarbonate and insulin with dextrose, respectively. Treatment should be guided by regular blood gas and electrolyte measurements. A diuresis should follow the infusion of cold fluid and mannitol (contained in the dantrolene bottle)

but further mannitol can be given if urine output is unsatisfactory. In order to limit renal tubular damage by myoglobin, it is important to maintain a diuresis of at least $2 \text{ ml kg}^{-1} \text{ h}^{-1}$, preferably with alkalinised urine. Coagulopathies and arrhythmias should be treated in the conventional manner, although calcium channel blocking drugs should not be used because, in combination with dantrolene, they can produce marked cardiac depression.

A poster describing guidelines for the emergency treatment of a MH crisis can be obtained from the Association of Anaesthetists of Great Britain and Ireland.

Patient counselling and referral

Following successful treatment of a suspected MH reaction, it is imperative that the patient is referred for confirmation of the clinical diagnosis. In the meantime, the full implications of the potential diagnosis should be made clear to the patient and family. Full details of the patient's reaction, all charts and results of investigations (including a 24 h postoperative plasma CK concentration) should be forwarded.

Confirmation of diagnosis

The mainstay of MH diagnosis is *in vitro* contracture testing (IVCT) performed at specialist centres. As living tissue is required, the patient must attend the centre for a muscle biopsy and subsequent pharmacological testing of fresh muscle strips. Tissue is excised from the vastus muscle, usually under regional anaesthesia. The tests involve measurement of the tension generated in response to separate exposures to halothane and caffeine. Compared with normal individuals, the tension in muscle from MH susceptible patients increases at lower halothane and caffeine concentrations.

Once a case is confirmed, further family members are investigated in the same way, starting with first degree relatives.

DNA diagnosis for MH has recently been introduced. However, this is on a limited basis because of the complexities of the genetics of MH (see later). It complements the standard IVCT method and cannot be used in isolation at the present time. New referrals (proband) who have been confirmed as MH susceptible by IVCT will have their DNA, obtained from venous blood samples, screened for the 15 'causative' mutations in the RYR1 gene currently stipulated for diagnostic purposes by the European MH Group guidelines. Should the proband carry one of these mutations, it can be used as an initial screening test for family members. If the family member carries the familial

Table 2 Triggers and safe drugs in malignant hyperthermia

Triggers (must be avoided)	Safe drugs
Halothane	Nitrous oxide
Enflurane	All intravenous anaesthetics, including ketamine
Isoflurane	All benzodiazepines
Sevoflurane	All non-depolarising neuromuscular blocking drugs
Desflurane	
Succinylcholine	All local anaesthetics, including preparations containing vasoconstrictors
	All analgesics, including opioids
	Neostigmine
	Atropine
	Glycopyrrolate
	Metoclopramide
	Droperidol

'Safe drugs' have been evaluated in the laboratory and safely used in patients known to be susceptible to malignant hyperthermia. Other drugs used in the context of anaesthesia have not necessarily been so thoroughly tested. Readers are advised to seek expert opinion from the Leeds MH Investigation Unit should they consider using other drugs in susceptible patients.

mutation, this confirms their susceptibility to MH without the need for a muscle biopsy. However, if the mutation is not present, a biopsy is still required as it is not safe to reject the diagnosis on DNA testing alone.

Anaesthesia for susceptible patients

MH patients requiring surgery should not be denied anaesthesia. Triggering drugs (all volatile anaesthetics and succinylcholine) should be avoided. Regional anaesthetic techniques are appropriate where feasible. For general anaesthesia, the anaesthetic machine can be prepared by removal of vapourisers and flushing through the machine and ventilator with 100% oxygen at maximal flows for 20–30 min. A new breathing circuit should be used. Triggers and drugs that have been established as safe in MH susceptible patients are listed in Table 2.

If these precautions are taken, the use of prophylactic dantrolene is not indicated as MH will not occur in the absence of a trigger. Dantrolene has side-effects, *e.g.* nausea, vomiting, muscle weakness (not usually clinically significant) and prolongation of the effect of non-depolarising muscle relaxants.

The genetics of malignant hyperthermia

Examination of the family tree of the first reported MH case indicated that the disorder was inherited in a classical autosomal

dominant fashion. However, application of state-of-the-art molecular genetic techniques over the past 12 years has revealed that MH is a more complex disorder at the DNA level. The major structure implicated in the aetiology of MH is the calcium release channel of the sarcoplasmic reticulum. This is also known as the ryanodine receptor protein because of its affinity for the plant alkaloid ryanodine that was used to identify and isolate it.

There is a statistically significant association between inheritance of DNA markers for the gene coding for the ryanodine receptor protein (RYR1) and MH susceptibility in > 60% of families large enough for such analyses world-wide. More than 30 mutations of the gene have been found in these families. However, so far, only 15 have been shown to have any functional (causative) effect. Only these 15 are recommended for diagnostic purposes. There is an incidence of at least 2.5% of families in which there are discordant results between the DNA and IVCT data. Several other genetic loci not linked to RYR1 have been associated with MH in individual families. A mutation has been found in one of these, *i.e.* the gene coding for the major sub-unit of the t-tubular voltage sensor (dihydropyridine receptor) responsible for excitation-contraction coupling in skeletal muscle.

There remain many families in whom no genetic defect has been isolated. Until MH can be more clearly characterised in genetic terms, DNA analysis for clinical diagnosis must be used cautiously to reduce the incidence of false positive and false negative results. The current European MH Group guidelines for DNA testing have been designed to reduce the risk of false negatives, a potentially dangerous result. In the UK, it is estimated that approximately 25–30% of families could benefit from DNA diagnosis at the present time.

Conditions associated with malignant hyperthermia

Although many conditions have been claimed to be associated with MH, only central core disease (CCD), an inherited disorder characterised by peripheral muscle weakness, is truly associated. Patients with CCD should be considered as potential MH patients and referred for MH screening. Many neuromuscular diseases are associated with difficulties with anaesthetic agents in their own right. Indeed, a neuromuscular condition is often brought to light by an abnormal response to anaesthesia. Therefore, histological examination is an important part of the muscle biopsy procedure in order to exclude underlying muscle disease, particularly a myotonic condition. Sudden infant death syndrome is no longer considered to be associated with MH. The association with heat stroke remains to be resolved.

Key references

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See multiple choice questions 5–9.