

Malignant hyperthermia

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Summary

Malignant hyperthermia (MH) is a rare but potentially fatal condition triggered by suxamethonium or an anaesthetic vapour. Early recognition of signs and prompt treatment are essential. The pathophysiology, clinical features and treatment of MH are described, with an emphasis on management and prevention in poorly-resourced settings.

INTRODUCTION

Malignant hyperthermia (MH) is a rare condition that was first recognised in the 1960s when a young man presenting for repair of a fractured tibia and fibula was more concerned about the anaesthesia than the operation. It transpired that 10 of his relatives had died following anaesthesia with ether. He subsequently went on to have a mild reaction to halothane anaesthesia.¹ Analysis of the family tree of this patient indicated an abnormal response to anaesthesia that was inherited via a dominant gene with incomplete penetrance. Much has been elucidated about MH since that time. There is good understanding of the cellular basis for MH, there is a specific treatment agent (dantrolene), an in vitro test for susceptibility to the condition has been developed and the specific gene defect has been identified. However, MH remains a condition that has the potential to be rapidly fatal in an otherwise fit and healthy individual. Anaesthetists should be aware of the diagnosis and treatment of this condition, the need to avoid specific trigger agents, and they should be able to provide safe anaesthesia for a patient who is susceptible to MH.

The actual incidence of MH cases has been reported to be between 1:5,000 and 1:50,000-1:100,000 general anaesthetics, but the prevalence of susceptibility to MH is felt to be much higher at about 1:3,000.² Due to its genetic basis, the prevalence of MH susceptibility varies around the world, and case reports or series have been reported for most ethnic groups including black Africans,^{3,4,5} Thai,⁶ Chinese,^{7,8} Japanese⁹ and Brazilians.¹⁰

PATHOPHYSIOLOGY OF MALIGNANT HYPERTHERMIA

The primary problem in MH is an inherited disorder of calcium handling in the sarcoplasmic reticulum of skeletal muscle. The genetic defect

is found on the gene encoding the intracellular ryanodine receptor, responsible for calcium release in skeletal muscle cells. In response to potent volatile anaesthetics and depolarising muscle relaxants the uncontrolled release of intracellular calcium leads to muscle rigidity, a hypermetabolic state and a build up of the breakdown products of skeletal muscle.

When suxamethonium is used, the first sign may be masseter spasm, where the jaw is clenched tightly after administration, preventing intubation or airway manoeuvres. Not all cases of masseter spasm will go on to develop MH, but all should be treated with a high degree of suspicion. If possible, further investigation for MH in all cases of masseter spasm is advised, since some will prove to have susceptibility despite the lack of a subsequent reaction.

Without treatment, MH can lead to multi-organ failure and death. Muscle breakdown products accumulate (rhabdomyolysis), leading to hyperkalaemia and myoglobinuria. Enzymes from skeletal muscle can cause renal failure, cardiac failure and disseminated intravascular coagulation. Renal failure exacerbates the hyperkalaemia and acidosis from rhabdomyolysis. The combination of hyperkalaemia, acidosis and hyperthermia lead to a high risk of fatal myocardial arrhythmias. Otherwise, renal failure as a consequence of rhabdomyolysis may prove to be fatal, particularly where there are no facilities for renal replacement therapy.

Initially mortality from MH was about 80%. Improved recognition and improvements in anaesthetic monitoring have helped to reduce mortality. Outcomes have improved significantly since the introduction of dantrolene, a specific treatment for MH, with no deaths reported in a series of New Zealand cases since dantrolene became available in 1981.¹¹ Mortality in countries

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with limited access to dantrolene may still be significant, with a mortality of 25.8% in Taiwan between 1994 and 2004.¹²

MH is linked to some rare myopathies. Central core disease (CCD), a rare non-progressive autosomal dominantly inherited myopathy has been shown to be linked to RYR-1 mutations in 93% of Japanese patients.² Patients typically present in infancy with hypotonia and proximal muscle weakness. CCD is closely linked to MH susceptibility by in-vitro contracture testing. However, the link is variable, and there are other rare mutations associated with central core disease.

CASE SCENARIO

A 24-year-old male of Maori origin presented for open appendicectomy as an emergency. The patient had no past medical history of note, no previous anaesthetics and denied any family history of anaesthetic complications.

A rapid sequence induction was performed with alfentanil, thiopentone and suxamethonium. Intubation was awkward with some muscle tension noted, but not overt masseter spasm.

Mechanical ventilation was instituted, but relatively high pressures were required for ventilation and the end-tidal (ET) CO₂ rose to 9-10.5kPa (70-80mmHg). The patient's pulse was 70-80bpm and the blood pressure was stable at 100-120mmHg systolic. Nasopharyngeal temperature was 36.5°C.

Ventilation was increased but ETCO₂ increased to 12kPa (90mmHg). His temperature increased to 37.5°C over half an hour. The surgeon commented on a degree of muscle tension despite neuromuscular blockade with rocuronium. Anaesthesia was completed with intravenous propofol, the soda lime and circuit were changed, surgery was expedited and cold packs were applied to groin and axillae. The MH trolley was brought into theatre and senior help was summoned. The mixing of the first dose of dantrolene was commenced.

There was no further rise in ETCO₂ or temperature. An initial arterial blood gas showed supranormal oxygenation, respiratory acidosis with metabolic compensation and a lactate less than 2.0. The ETCO₂ at this point had fallen to 60mmHg (9kPa). The decision was therefore taken not to administer dantrolene and to wake the patient. He was extubated awake and kept in recovery for about 1 hour, where he complained of generalised muscle pains. He was then transferred to the High Dependency Unit. Initial bloods showed normal renal function and full blood count, with a creatine kinase (CK) of 25,000iu.l⁻¹. Urinary myoglobin was positive and he was treated with hydration and alkalinisation of urine. By the morning CK had risen to 30,000iu.l⁻¹, but settled over the following three days, after which he was discharged to the ward. He was given verbal and written instructions regarding malignant hyperthermia and referred for testing at a regional centre. Testing at 6 months post-event showed a strongly positive contracture test to both halothane and caffeine.

Also associated with MH are myotonia fluctuans, Multiminiore disease, Multiminiore myopathy, King Denborough syndrome and hypokalaemic periodic paralysis.²

CLINICAL FEATURES

Immediate changes

The presentation of MH is variable, but if a patient develops the signs of a hypermetabolic state or abnormal muscle rigidity under anaesthesia, then this should lead the anaesthetist to have a high index of suspicion.

Masseter spasm may be a herald of MH in patients administered suxamethonium, but not all patients with masseter spasm develop MH. For those who do not have masseter spasm, a rise in end-tidal CO₂ (ETCO₂) is normally the first sign. Tachycardia or tachyarrhythmia may be the first sign in the absence of ETCO₂ monitoring.

A rise in temperature typically occurs later, but at least two patterns are demonstrated, either an early rapid rise in temperature over a period of minutes, or alternatively a slow rising temperature which becomes apparent after about an hour. The temperature may rise more than 2°C per hour in fulminant MH.²

Other features of MH include:

- *Muscle rigidity* unaffected by neuromuscular blockade.
- *Cyanosis* develops with an increased oxygen extraction ratio. Oxygen consumption may increase up to threefold leading to cellular hypoxia despite a supranormal oxygen delivery. Increased end-tidal (i.e. alveolar) CO₂ leads to displacement of oxygen in the alveolus, as described by the alveolar gas equation ($PAO_2 = PiO_2 - [PACO_2/R]$), reducing alveolar O₂ despite an adequate FiO₂.
- *Arrhythmias* – predominantly ventricular.
- Hypoxia, hyperkalaemia, metabolic acidosis and hypocalcaemia.

Late complications

Later complications are a result of rhabdomyolysis. Patients can go on to develop multi-organ failure as a result of a combination of rhabdomyolysis, electrolyte abnormalities and hyperthermia, leading to death.

Malignant hyperthermia may not be identified during a first anaesthetic and commonly presents during a second or third anaesthetic.

DIFFERENTIAL DIAGNOSES OF MALIGNANT HYPERTHERMIA

Other causes of a hypermetabolic state should be considered in the differential diagnosis:

- **Sepsis.**
- **Thyroid storm.**
- **Neuroleptic malignant syndrome** presents with hyperthermia and rigidity, typically developing hours to days after introduction of a neuroleptic drug. The pathogenesis is related to central dopamine handling rather than peripheral calcium channel effects. Treatment consists of a dopamine agonist (L-dopa or bromocriptine), but dantrolene may be required.

TREATMENT

A high index of suspicion for the diagnosis is important, as the management of malignant hyperthermia is dependant on early detection. On suspicion of MH, treatment should be instituted immediately, prior to confirmatory tests.

Effective treatment requires the immediate withdrawal of trigger agents (volatile agents), the administration of dantrolene, and the quick and effective actions of a well-trained team. Assistance is required for the management of such a rapidly deteriorating patient, including for the mixing of dantrolene, which is time-consuming.

Treatment falls into **immediate management** to halt the process and treat the immediate metabolic effects of MH, **ICU management** to continue resuscitation, manage the effects of rhabdomyolysis and observe for complications and **further management** aimed at investigation and advice for both patient and family.

Immediate management

Removal of trigger agents

Volatile anaesthesia should be discontinued and no further doses of suxamethonium should be used (particularly when masseter spasm is encountered at rapid sequence induction). A high fresh gas flow, preferably 100% O₂ should be used to flush the anaesthetic machine and ideally the breathing circuit should be replaced with a clean circuit. Anaesthesia will need to be maintained with intravenous agents (ketamine, thiopentone, propofol and opiates are all safe to use). The end of surgery should be expedited in order to focus on the management of MH.

Muscle relaxation

Non-depolarising muscle relaxants such as pancuronium or vecuronium are ineffective in reducing muscle contraction in MH as the pathology is intracellular. Dantrolene has an inhibitory effect on the ryanodine receptors on the sarcoplasmic reticulum of skeletal muscle, inhibiting calcium ion release. It is a specific antagonist to the MH process. Powder for reconstitution contains mannitol and sodium hydroxide to enhance solubility and increase pH. The Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines

suggest a dose of 2-3mg/kg initially, followed by 1mg/kg up to every 10 minutes as required to reduce muscle contraction.¹³ It is time-consuming to mix dantrolene so it is advisable that this role is delegated.

In the absence of dantrolene, treatment will be predominantly supportive, removing trigger agents and concentrating on the cooling measures described below.

Cooling

Active cooling is likely to be necessary, particularly where dantrolene is not available, but vasoconstriction by excessive cooling of the peripheries should be avoided. Active warming devices such as hot air mattresses can be converted to cooling mode, cold intravenous fluids should be used and consideration should be given to cold bladder irrigation and cold peritoneal lavage, particularly if the abdomen is already open as part of the surgery. Cold packs can be used, but should only be used in areas of high blood flow where tissue damage is less likely (not around the peripheral limbs). Sites where cold packs are placed should be inspected and duration of application should be limited.

Hypoxia and acidosis

The patient should be hyperventilated to, as close as possible, a normal pH. An adequate FiO₂ to maintain good oxygenation, despite the high metabolic demands, is needed – 100% oxygen is advisable initially. Sodium bicarbonate helps treat the acidosis and enhances the solubility of myoglobin by forced alkaline diuresis.

Rhabdomyolysis

Adequate hydration and alkalinisation of the urine help to solubilise myoglobin released from skeletal muscle, reducing the risk of renal failure. Aim for a urine output >3ml.kg⁻¹.h⁻¹ and a urine pH>7.0.¹³

Hyperkalaemia

Hyperkalaemia should be managed if serum potassium exceeds 6.5mmol/l or is felt to be contributing to arrhythmias.

- Polystyrene sulphonate resins (e.g. **calcium resonium**), 15g orally or 30g rectally, 6-8 hourly bind and remove potassium, but are relatively slow-acting in acute episodes.
- **Insulin** 15 units in 100ml of 20% **glucose** IV over 30-60 minutes drives potassium into the cells. (Roughly equivalent regimens using more or less concentrated glucose eg. 50ml of 50% glucose or 200ml of 10% glucose will have the same effect).
- **Bicarbonate** 50mmol IV leads to exchange of potassium for hydrogen ions across cell membranes and is particularly effective at reducing hyperkalaemia in the presence of acidosis.

- **Salbutamol** (a β_2 -agonist) 5mg nebulised, 50mcg IV bolus or 5-10mcg/min IVI increases cellular uptake of potassium.
- **Calcium** 5-10ml of 10% calcium gluconate, or 3-5ml of 10% calcium chloride has a rapid onset, but a short duration of action, acting as a physiological antagonist to potassium.
- **Haemodialysis**, where available, may be required to clear potassium and for management of renal failure in some cases.
- Presentation is often with intractable pain from tissue ischaemia (masked in unconscious patients).
- Other signs include
 - Tight tissues
 - Distal limb ischaemia
 - Absence of distal pulses
- Compartment pressures can be measured with a manometer, via a needle.
- Treatment consists of surgical fasciectomy

Cardiac arrhythmias

Sinus tachycardia with or without ventricular ectopic beats is common in MH, and may be the presenting feature. More serious arrhythmias can occur, especially VT and VF.

- **Procainamide** is useful for both ventricular and supraventricular arrhythmias and can be given IV at 25-50mg/min, up to a maximum of 1g. The ECG should be monitored for widened QRS and prolonged PR interval.
- **Magnesium sulphate** is useful for ventricular arrhythmias in a dose of 2g IV over 10 minutes.
- **Amiodarone** can be useful for both ventricular and supraventricular arrhythmias with a loading dose of 5mg/kg over 1 hour (roughly 300mg), followed by an infusion not exceeding 1.2g in 24h.

Calcium channel antagonists should be avoided in a MH crisis.

Disseminated intravascular coagulation

Conventional treatment with clotting factors (fresh frozen plasma, cryoprecipitate and platelets) as dictated by blood tests is used.

Management in ICU

Continuation of the treatments above is likely to be necessary, potentially including further doses of dantrolene for up to 24h. Care should be in a high dependency setting, where frequent monitoring can be continued, as well as intensive therapy. Reactivation can occur for up to 24h and active monitoring to detect this is necessary.

In addition to the above specific treatment, it is necessary to offer general supportive therapy and particularly to observe for and treat *renal failure* and *compartment syndrome*.

Compartment syndrome is a result of tissue damage in a limiting fascial sheath, with swelling and oedema leading to compression of the tissues and structures. High tissue pressures lead to further tissue necrosis and can obstruct blood flow to distal tissue.

- Common sites are calves and forearms.

Further management

The patient should be referred to a specialist centre for MH testing if possible. If MH testing is not possible, the MH grading scale can be used to assess the likelihood of this having been a genuine episode of MH.¹⁴ There is no strict cut-off to define the diagnosis, but, coupled with clinical judgement, the MH grading scale has been found to be useful. The scale is based on clinical and common biochemical markers and provides a likelihood range from almost never (0 points) to almost certain (50+ points). Marks are scored for rigidity, evidence of muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement, family history and a miscellaneous section (acidosis and reversal with dantrolene). The validity of the scale has been questioned since the introduction of in vitro contracture testing into common use,¹⁵ but no other clinical scale has been suggested as a replacement.

The patient and family should be counselled regarding the implications of MH. It is important that this is explained prior to discharge from hospital and this is the responsibility of the anaesthetic team.

With a diagnosis of MH there is a 50% chance of any parent, child or sibling having MH, and they should be appropriately counselled, and regarded as MH positive until negative testing is available. Aunts and uncles have a 25% chance and first cousins have a 12.5% chance of having MH. Accurate mapping in the absence of genetic testing can be difficult, but a detailed family history may help to elucidate the affected family. In the absence of testing, where there is a high suspicion of risk, the use of a volatile and suxamethonium-free anaesthetic should be seriously considered, and it would be wise to have a very high clinical suspicion for MH.

The gold standard test for MH is still the in vitro contractility test to halothane and caffeine. This requires a muscle biopsy to be taken under local anaesthesia (or using a trigger-free anaesthetic), six months after the event. Genetic testing is possible once the specific genotype is known from a family member. However, in order to definitively exclude MH susceptibility in a subject, in vitro contracture testing is still required.

ANAESTHESIA IN PATIENTS SUSCEPTIBLE TO MH

The key to anaesthesia in susceptible patients is to avoid the possible MH trigger agents, suxamethonium and volatile anaesthetics.

Due to the widespread use of volatile agents in theatres, it is important to ensure decontamination of the anaesthetic machine. A volatile-free machine can be kept in the theatre complex for such an occasion (and can also be used for critically ill patients in recovery), however, this is expensive and unnecessary. Alternatively, it is possible to ensure that the machine to be used is adequately cleared of volatile anaesthetic agents by flushing it through with 100% oxygen. The period required to flush the machine will depend on the machine used as well as the amount of componentry and circuitry changed. While the time required at 10 l/min may be as little as 5 minutes with some machines, after changing a large portion of the components, a minimum of 30 minutes seems wise, with 60 minutes of flushing appearing safe in almost all circumstances. If using a circle system, it is advisable to change the patient circuit and soda lime.

Black rubber absorbs anaesthetic vapours and should be changed to a fresh circuit prior to use for patients with known susceptibility to MH when possible, but a 20 minute flush with at least 8 l/min oxygen gives outflow concentrations of less than 5 ppm halothane in previously contaminated rubber circuits.¹⁶ High fresh gas flows are required not only to flush the machine, but also to ensure volatile concentration doesn't subsequently rise. It should be noted that a recovery area with previously anaesthetised patients has been shown to have concentrations as high as 1 part-per-million halothane,¹⁷ so complete exclusion of volatile is likely to be impossible.

Anaesthesia can be safely administered with intravenous agents and a non-depolarising agents such as vecuronium, pancuronium or rocuronium.

Where feasible for the planned surgery, spinal or regional anaesthesia are safe and appropriate techniques in patients who are MH susceptible, but safe emergency anaesthetic circuits and drugs should always be available for such a patient should general anaesthesia become necessary.

In addition to a trigger-free anaesthetic, it is important to monitor the patient carefully to detect possible activation of MH during anaesthesia or recovery. Monitors should include ET_{CO}₂ during anaesthesia and temperature monitoring during anaesthesia and recovery.

A pre-prepared MH trolley (a station with the necessary equipment for dealing with MH, including dantrolene, sterile water, sodium bicarbonate and cooling packs) should be immediately available throughout the procedure and recovery. The duration of postoperative monitoring is controversial,

however 1 hour in recovery appears to be a safe period, and for day surgery patients, a further one and a half hours prior to hospital discharge.

REFERENCES

1. Denborough, MA, Forster JFA, Lovell RRH, Maplestone PA and Villiers JD *Br J Anaesth.* 1962; **34**(6): 395-396.
2. Rosenberg H, Davis M, James D, Pollock N, Stowell K: Malignant hyperthermia; *Orphanet Journal of Rare Diseases* 2007; **2**:21.
3. PetizB, Carstens J. An unusual case of malignant hyperpyrexia. First case report in a South African negro. *Anaesthesia.* 1975 May; **30**(3): 346-350.
4. Rizk SF. Malignant hyperpyrexia in a negro. *Br J Anaesth* 1973 Feb; **45**(2): 233.
5. Lombard TP, Couper JL. Malignant hyperthermia in a black adolescent: A case report. *S Afr Med J* 1988 Jun; **73**(12): 726-9.
6. Pulnitipom A, Charuluxananan S, Inphum P, Kitsampanwong W. Malignant hyperthermia: a case report in Thai Anesthesia Incidents Study (THAI Study) *J Med Assoc Thai* 2005 Nov; **88** (Suppl 7): S149-52.
7. Yu ZH, Loo AL, Guo XY, Ren HZ, Wang YL, Zhang X, Huang YG, Ye TH. Malignant hyperthermia in China. *Anaesth analg.* 2006 Oct; **103**(4): 983-5.
8. Leung AK. Malignant hyperthermia in Chinese children. *Oral Surg Oral Med Oral Pathol* 1987 Mar; **63**(3): 317.
9. Maelusa Y, MukaidaK, Morio M, Kawamoto M, Yuge O. Genetic analysis with Ca²⁺ induced Ca²⁺ release test in Japanese malignant hyperthermia susceptible (MHS) families. *Hiroshima J Med Sci* 1999 Mar; **98**(1): 9-15.
10. McWilliams S, Nelson T, Sudo RT, Zapato-Sudo G, Baiti M, Sambuughin N. Novel skeletal muscle ryanodine receptor mutation in a large Brazilian family with malignant hyperthermia. *Clin Genet* 2002 Jul; **62**(1): 80-3.
11. Pollock AN, Langton EE, Couchman K, Stowell KM, Waddington M: Suspected malignant hyperthermia reactions in New Zealand; *Anaesth Intensive Care* 2002; **30**: 453-461.
12. Yip WH, Mingi CL, Ooi SJ, Chen SC, Chiang YY: A Survey for prevention and treatment of Malignant Hyperthermia in Taiwan; *ACTA Anaesthesiol Taiwan* 2004; **42**(3):147-51.
13. Association of Anaesthetists of Great Britain and Ireland. Guidelines for the management of a malignant hyperthermia crisis. 2007. Available from <http://www.aagbi.org/publications/guidelines/docs.malignanthyp07amended.pdf>
14. Larach MD, Localio AR, Allen GC, Denborough MA, Ellis FR, Gronert GA, Kaplan RF, Muldoon SM, Nelson TE, Ordning H, Rosenberg H, Waud BE, Wedel DJ. A Clinical Grading Scale to Predict Malignant Hyperthermia Susceptibility. *Anesthesiology* 1994 Apr; **80**(4): 771-9
15. von Richthofen V, Wappler F, Scholz J, Fiege M, Schulte am Esch J [Evaluation of malignant hyperthermia episodes with the Clinical Grading Scale] *Anesthesiol Intensivmed Notfallmed Schmerzther.* 1998 Apr; **33**(4): 244-9.
16. Gilly H, Weindlmayr-Goettel M, Köberl G, Steinbereithner K. Anaesthetic uptake and washout characteristics of patient circuit tubing with special regard to current decontamination techniques. *Acta Anaesthesiol Scand.* 1992 Oct; **36**(7): 621-7.
17. Ritchie PA, Cheshire MA, Pearce NH. Decontamination of halothane from anaesthetic machines achieved by continuous flushing with oxygen. *Br J Anaesth.* 1988 Jun; **60**(7): 859-63.