

MALIGNANT HYPERTHERMIA

Dr Neil Pollock

Palmerston North Hospital
Palmerston North

Malignant hyperthermia (MH) is an inherited uncommon hypermetabolic disorder caused by dysfunctional Ca homeostasis in skeletal muscle and triggered almost exclusively by potent inhalational agents and depolarising muscle relaxants. It has autosomal dominant inheritance.

All known MH reactions in NZ have been documented. Masseter spasm is the earliest sign and only occurs when suxamethonium has been administered and has only been present in 22% of NZ MH reactions. If masseter rigidity is excluded, increased ETCO₂ accounts for over 90% of the first signs of an MH reaction. Tachycardia defined as a HR of >100/min is almost always present and supraventricular arrhythmias, bigeminy or ectopics are seen in 23%.

Temperature is sometimes published as a late sign but Larach (2008) recently reviewed NA MH Registry data and found that in 161/255 patients or 63% temperature increase was 1st-3rd sign of an MH reaction. Temperature exceeded 38.8°C and was regarded as inappropriately rapidly increasing.

Rigidity and particularly acidosis were prominent signs of MH reactions several decades ago mainly because the diagnosis was made late. Wappler (2001) has found that in Germany the average base deficit is 5-7mmol/litre. In NZ MH reactions over the last 2 decades, base deficit or excess ranged from (-10- +1). Hyperkalaemia can be a feature. If the reaction is not treated, increasing temperature (46°C), tachycardia, hyperkalaemia, hypoxia, DIC, cardiac arrest will result. The current mortality worldwide is less than 5%.

Creatine kinase can increase to over 200,000 although dantrolene damps down this response. There is no real evidence that isolated rhabdomyolysis developing up to 24 hours following anaesthesia indicates MH susceptibility. However further neurological investigation is warranted in a case of isolated rhabdomyolysis.

Postoperative MH

There are a number of reports in the 1970/80s of MH reactions first identified in recovery when awareness of MH and monitoring were limited. The US MH 'Hotline' established in 1987, receives frequent calls for advice on suspected postoperative MH reactions. The most commonly reported signs are tachycardia, tachypnoea, rigidity, hypercarbia and pyrexia and rhabdomyolysis. Litman (2008) reviewed 528 suspected MH reactions held by NA MH registry. Ten were regarded as developing in PACU and the first sign of all developed within 16 minutes of transfer to PACU with one exception which developed about 30 minutes post transfer, so this is an uncommon event.

A further 3 studies have examined postoperative pyrexia (41.5°C) and MH susceptibility. The pyrexia developed mostly within 24 hours postoperatively, and examples of the histories given were repeat pyrexia, family history of pyrexia, 'packed in ice', 'fanned', ICU admission with temperature. All 3 studies demonstrated normal muscle biopsies.

If a patient has stable observations on discharge from recovery and subsequently develops signs which could be associated with MH particularly a temperature this is extremely unlikely to be an MH reaction.

Triggering Factors

All potent inhalational agents including sevoflurane and desflurane, suxamethonium and extremely rarely, stress.



Will the use of Sugammadex eliminate the need for suxamethonium and reduce the incidence of MH reactions? Possibly but it won't eliminate MH while potent inhalational agents are still in use.

In NZ about one third trigger with inhalational agents alone and an unknown number may still have developed without the use of suxamethonium.

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Management

Management is well detailed on this poster distributed by Pfizer. The poster is part of a resource kit developed by the MHANZ group, which contains suggestions for the management of MH. The resource kit can be accessed from the MHANZ website - www.malignanthyperthermia.com.au

Dantrolene is the mainstay of treatment, an initial dose of 2.5 mg/kg

Cooling is best achieved with (1) iv saline at 4°C – one litre reduces temp by 0.5°C and (2) packing exposed surfaces with ice, (3) Peritoneal lavage, (4) dantrolene. Amiodarone is first choice for arrhythmias. Treat hyperkalaemia, acidosis.

Admission to ICU is essential as recurrence can develop in up to 25% after initial treatment. Recommended dantrolene supply – 24 x 20mg vials. This is equivalent to about 2 x 2.5mg/kg doses in a 100kg individual. For large hospitals – 36 vials. (ANZCA Professional document – 'Recommendations on minimum facilities for safe administration of anaesthesia in operating suites and other locations' 3.2.4).

Tests for Susceptibility

DNA Analysis

DNA analysis was first described in 1990. Mutations in the genes encoding the ryanodine receptor (ryr1) receptor are associated with MH and can lead to defective formation of the receptor. Mutations are identified by PCR and automated sequencing.

Mutations can be (a) silent, the DNA is altered but no change in the receptor, (b) change the amino acid sequence in the receptor with no change in function – polymorphism, (c) result in change in function of the receptor such as increased Ca²⁺ release in the case of MH. If other criteria are fulfilled, the mutation is regarded as a causative mutation. Only 29 causative mutations have been identified so far and a positive DNA test for a causative mutation indicates MH susceptibility.

Even in the most advanced European research units a causative mutation has been identified in only 50% of families so there are still more to identify. Some families have multiple mutations so until all possible mutations are identified a negative DNA test has to be supported by a negative muscle biopsy.

Genetic linkage analysis indicates that not all mutations are located in the ryr1 gene. One causative mutation has been identified in the dihydropyridine gene and the remainder are unknown. Calsequestrin is a binding protein located within the SR terminal cisternae. It serves to concentrate Ca²⁺ ions near the site of release from the ryanodine receptor. Deletions of the gene in a genetically engineered mouse, the 'knockout mouse' result in a rapidly fatal fulminant MH reaction when the mouse is exposed to halothane (Dainese 2009). Pre treatment with dantrolene helps to prevent this. This is really the first evidence that a defect in an associated protein of Ca release may be associated with MH and further developments will be watched with interest.

IVCT

The in vitro contracture test was developed in 1970 and remains the gold standard of testing. Results are divided into 3 categories – MHS - susceptible, MHE- equivocal, MHN-normal.

How reliable is the test? - only the MHN results are discussed. There are a number of reports of false negative results in the anaesthetic literature but if these are examined carefully there are other possible explanations such



as concurrent sepsis, non standard method of testing and coexistent myopathy. There have been no anecdotal reports of false negative results in NZ or Australia and to confirm this, a study was undertaken to examine as many records as possible just to confirm the reliability of MHN diagnoses.

Patients were obtained from the PN MH database, anaesthetic records retrieved from throughout NZ and ethical approval obtained. Study population included MHN patients and immediate relatives who are regarded as not susceptible.

162 MHN/relatives received 322 triggering anaesthetics. Ages ranged from 1-79 years and anaesthetic time 15 minutes – 10+ hours. Multiple triggering agents were used. There was no evidence of an MH reaction. Negative DNA tests were available for 55% of anaesthetic records supporting the reliability of MHN diagnoses. This study does show that MHN test results are reliable, it is not statistically significant but it does give an indication that it is safe to give triggering agents to MHN individuals.

Elective Management

- Preoperative assessment – check IVCT status, exclude associated disorders, review previous records where possible, assess airway. ‘Cousins’ are not always blood relatives.
- Premedication to reduce stress in an MH susceptible patient is not indicated.
- The highest safest concentration of inhalational agent is 5ppm demonstrated in susceptible swine (Maccani 1996). Washout of unscavenged anaesthetic vapour is very rapid in well ventilated theatres (20 fac/hr) and achieves this level within a few minutes. The normal change around time between cases is sufficient. Peak halothane levels reached 1.5ppm in PN recovery with 14fac/hour.
- After removing vaporizer, circle tubing, reservoir bag, and changing absorber, newer anaesthesia machines require longer flush periods than older machines to achieve acceptable residual halogenated anaesthetic concs. e.g. Datex-Ohmeda Aestiva after saturation with 2% sevo for 2 hrs. requires 55 minutes flushing at 10l/min to achieve less than 5ppm.
- LMAs are reused in Palmerston North.
- Anaesthetic technique - Propofol infusion with an opioid and muscle relaxant are common anaesthetic techniques. Regional is used where indicated.
- Drugs safe to use. Ketamine, atropine, B agonists, digoxin, theophylline, caffeine, adrenaline.
- Chloro-m-cresol is a potent MH trigger and contained in many insulin preparations. It triggers MH in susceptible swine but only in doses about 150x higher than concentrations in these preparations.
- Postoperatively, standard management. A set of observations on immediate transfer to recovery followed by 2 further sets at 15 minute intervals and then discharge to ward, step down unit, home.

References

1. Larach M. Anesthesiology 2008 October 18 A374.
2. Wappler F Eur J Anaesthesiology 2001; 18: 632-52.
3. Litman R. Anesthesiology 2008; 109: 825-9.
4. Dainese M Faseb Journal 2009; 23: 1-11.
5. Maccani R Anesth Analg 1996; 82: S287.

