Article:
Gupta, PK and Hopkins, PM orcid.org/0000-0002-8127-1739 (2017) Diagnosis and management of malignant hyperthermia. BJA Education, 17 (7). pp. 249-254. ISSN 2058-5349

https://doi.org/10.1093/bjaed/mkw079

Diagnosis and management of Malignant Hyperthermia

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RCoA CPD matrix:

(1A01); (2A06)

Keywords

Malignant hyperthermia; skeletal muscle; dantrolene

Introduction:

In this article we will first describe the epidemiology, pathophysiology, diagnosis and differential diagnosis of Malignant Hyperthermia (MH). We will then discuss the peri-operative management, referral and diagnosis of suspected MH. In order to set the scene and focus of the article it is useful to initially provide some definitions.

Definitions

Malignant Hyperthermia. Malignant hyperthermia is a progressive, life-threatening hyperthermic reaction occurring during general anaesthesia. A separate identity, with specific ICD codes, for a hyperthermic reaction occurring during general anaesthesia is required because other categories of heat illness require an assessment of cerebral function for their differential diagnosis.

Malignant Hyperthermia susceptibility. This describes the genetic predisposition to develop malignant hyperthermia under anaesthesia.

Epidemiology of MH

The occurrence of MH in Japan, China, Australia, America and Europe is well established. However, some communities still believe that MH does not affect their race. This is ascribed to anecdotal evidence i.e. presumed genetic isolation. The UK is a cosmopolitan country with immigrants from all over the world. Data from our national UK unit confirms the presence of MH susceptibility in individuals from Asia[1], Europe, the Middle East and Africa.

The first patient in a family to have a MH reaction is known as the index case or proband. Audit of the probands referred to the MH unit in Leeds (1990 – 2010) shows that MH reactions are more common in males (62%) than females (38%). Testing is offered to all family members of probands in whom MH susceptibility is confirmed. Of all patients tested for MH susceptibility at Leeds up to December 2014, 4085 were males and 4040 females. The incidence of a positive test result was

slightly higher in males (42%) than females (37%). The male preponderance of MH probands could be incidental as a consequence of more males requiring surgery than females or it may be that the clinical condition has higher clinical penetrance in males who are MH susceptible than females.

An MH reaction can occur at any age but the age distribution of probands is positively skewed with most reactions occurring in children or young adults. This may explain why the incidence of MH is noted to be greater after trauma, orthopaedics and ENT procedures.

Around 150 new patients are referred to the Leeds National UK MH Unit every year. Out of these, 40 to 50 patients test susceptible to MH. Considering that about 2.8 million anaesthetics[2] are performed in the UK every year, this translates into an approximate incidence of 1: 50,000 to 1: 70,000 for the UK population. The reported estimates of the prevalence of MH susceptibility range from 1:3,000[3] to 1: 100,000[4].

Many patients have had apparently uneventful general anaesthetics with triggering agents prior to the occasion when they have an MH reaction[5]. The reasons for this are not entirely clear but it could be related to the duration of surgery, the choice of the volatile anaesthetic agent and the concentration of the agent delivered during the surgery. In the UK a patient developed an MH reaction on their 13th exposure to general anaesthesia, while in USA, a patient developed an MH reaction on their 31st exposure.

The mortality from MH in the UK is 4%[6], while the most recent data from the USA suggest that the mortality from MH reactions there has increased over the last 15 years to 6 -12%[7]. The reasons for this are likely to be multifactorial but the increased number of “office-based” procedures and a misplaced presumption that MH is always treatable may be important. In recent years MH reactions, including fatal reactions in the UK, have resulted from the use of inhalation agents for sedation or the treatment of status asthmaticus in the ICU.

Pathophysiology:

Knowledge of the basic physiology of skeletal muscle contraction is required for an understanding of the pathophysiology of an MH reaction. An action potential is generated at the motor endplate when a nerve impulse arrives at the neuromuscular junction, acetylcholine is released and binds to its receptor. The action potential spreads across the skeletal muscle membrane, including its invaginations, the T-tubules. Within the T-tubules, voltage sensors, known as dihydropyridine receptors (DHPR) undergo a conformational change in response to the arrival of the action potential. The conformational change in the DHPR involves an intracytoplasmic loop of the protein, which consequently interacts with the calcium release channel of the sarcoplasmic reticulum (SR), which is a ryanodine receptor (RyR) isoform. The calcium ion conducting pore of the RyR opens and calcium is released into the cytosol. The calcium ions bind to troponin C on the thin myofilaments enabling cross bridge formation between actin and myosin and muscle contraction. The cross bridge cycle requires energy which is provided by ATP. Actin-myosin cross bridging converts only approximately 40% of energy used into work, the rest generating heat. When the muscle contracts it utilises oxygen and releases CO_2. Under normal circumstances calcium is actively sequestered out of the cytosol with further utilisation of ATP, decreasing cytosolic calcium concentration and enabling the muscle to relax.

The transduction of the electrical energy into the mechanical work of muscle contraction is known as excitation-contraction (EC) coupling. In patients susceptible to MH, exposure to trigger agents leads to dysregulation of EC coupling and a sustained release of calcium into the cytosol. Initially this causes an increased metabolic demand for ATP to sequester the calcium, causing an increase in CO_2 production and O_2 consumption. The rise in CO_2 stimulates the sympathetic nervous system thereby causing a reactive rise in the heart rate. As the release of calcium progresses, sequestration capacity is exceeded and cytosolic calcium accumulates sufficiently to activate the myofilaments and cause muscle contraction. In this phase of the reaction heat production accelerates and progressive muscle rigidity develops (Fig. 1). The initial acid-base disturbance is a respiratory acidosis. When oxygen demand exceeds supply lactate levels will rise and a metabolic component will be

superimposed on the respiratory acidosis. Sustained contractile activity perturbs sarcolemmal integrity causing the release of potassium ions, creatine kinase and myoglobin leading to hyperkalaemia and acute kidney injury. Hyperthermia and rhabdomyolysis predispose to disseminated intravascular coagulation.

Figure 1 near here

At the molecular level, the most common defects leading to MH susceptibility are mutations in RYR1, the gene encoding the skeletal muscle isoform of RyR: these account for 40-80 % of cases. Approximately 1% of cases result from mutations in CACNA1S, the gene encoding the principal subunit of the DHPR. The genetic causes of the remaining cases have not yet been identified.

Table 1 near here

Clinical presentation of Malignant Hyperthermia.

From the above account of the pathophysiological process it will be apparent that the cardinal and most consistent clinical features of an MH reaction are a rise in end-tidal CO_2 ($ETCO_2$) (tachypnoea if the patient is breathing spontaneously), unexplained increase in heart rate, rise in core body temperature and muscle rigidity. While the order of onset of these features of an MH reaction is consistent between cases, their temporal separation and relative magnitude is variable. Some of this variability is poorly understood but known factors include whether succinylcholine precedes inhalational anaesthesia (succinylcholine accelerates the course of the reaction), the choice of inhalational anaesthetic (the greater the anaesthetic potency, the greater is the tendency for a quicker onset and more rapid course, i.e., isoflurane>sevoflurane>desflurane), the use of drugs that reduce sympathetic heart rate responses (beta-blockers, remifentanil), and the baseline core body temperature.

If a malignant hyperthermia reaction is allowed to proceed unchecked, the metabolic hyperactivity and muscle breakdown will lead to progressive hypercapnoea, increase in heart rate, hyperthermia, muscle rigidity, rhabdomyolysis, hyperkalaemia, acidosis, hypoxia and DIC. The combination of hypercarbia, sympathetic stimulation, hyperkalaemia and acidosis is highly arrhythmogenic and cardiac arrest should be anticipated unless arrhythmias can be rapidly corrected. An irreversible stage is associated with a combination of histotoxic hypoxia (mitochondrial failure) and stagnant hypoxia (muscle ischaemia caused by swollen necrotic muscles increasing intra-compartmental pressures).

Patients with genetic susceptibility to MH may present with other clinical features in the perioperative period that do not amount to a MH reaction. These are caused by an exaggerated stimulatory response to succinylcholine and include prolonged (> 2 min) and pronounced (unable to open mouth) jaw muscle rigidity, known as masseter muscle spasm, generalised muscle rigidity, and/or rhabdomyolysis. We are aware of one case where succinylcholine induced an acute hyperkalaemic cardiac arrest but the more common scenario is for rhabdomyolysis to present in the postoperative period as myoglobinuria and acute kidney injury.

The full spectrum of presentations in referrals to the Leeds MH Unit over a 45-year period can be broadly classified into 8 categories[8]:

1. Classical / Fulminant / Severe features of malignant hyperthermia: Indisputable evidence of marked metabolic hyperactivity and muscle breakdown. The reaction was life-threatening and active treatment for MH was administered.
2. Moderate features of malignant hyperthermia: features of metabolic hyperactivity and muscle breakdown consistent with MH but the reaction was terminated before it became life-threatening or the diagnosis certain.
3. Mild features of malignant hyperthermia: One or more metabolic signs of MH were observed but a full picture of MH did not develop.
4. Masseter muscle spasm as the sole feature.

5. Masseter spasm with evidence of rhabdomyolysis.
6. Masseter spasm with signs of metabolic disturbance.
7. Unexplained peri-operative death or cardiac arrest. Historically, about 2/3 of such referrals were found to be related to MH but with adequate and accurate medical records it should be possible to either exclude MH or allocate the presentation into one of the categories described above.
8. Others: Postoperative pyrexia, postoperative rhabdomyolysis. Pyrexia in the postoperative period is a common reason for referral to the Leeds MH Unit. There are reports of MH being diagnosed up to 40 minutes after the discontinuation of the inhalational anaesthetic trigger. It is likely that the features of MH were present but not recognised some time before the diagnosis was made. However, a raised body temperature in isolation is not indicative of MH because the rise in temperature is always preceded by metabolic stimulation. Therefore, if the full anaesthetic and recovery records can be sourced, it is possible to exclude MH in almost all cases of postoperative pyrexia. Alternatively, MH can be excluded if it can be established that the pyrexia occurred on the surgical ward rather than on the postoperative care unit.

The signs and symptoms of MH are not specific to MH. The differential diagnosis of MH is shown in table 2.

Table 2 near here

Clinical management

Early diagnosis can lead to a significant reduction in mortality and morbidity from MH[3]. Once MH is suspected, as much help as possible should be summoned as multiple simultaneous actions will be required to optimally manage the reaction. In the event that no immediate extra help is available consider using the surgeon and the scrub staff as additional pairs of hands.

Immediate management:

1. Anaesthesia:
    a. Stop administration of volatile anaesthetic agent, remove the vaporiser and hyperventilate with 100% oxygen to increase elimination of triggering agent and CO_2 and to maximise oxygen delivery.
    b. If activated charcoal filters are available, insert one filter at each of the inspiratory and expiratory ports and follow the manufacturer's instructions.
    c. If activated charcoal filters are not available:
        i. If sufficient personnel available, task one assistant to manually hyperventilate the patient's lungs using a non-rebreathing circuit, such as a self-inflating bag and oxygen while excess volatile agent is removed from the machine (soda lime removed, circle system flushed with maximum oxygen and air flows for 5 minutes, fresh soda lime inserted).
        ii. Otherwise, hyperventilate with 100% oxygen at 15 L/min. When sufficient skilled help arrives, change breathing circuits and soda lime (change of soda lime may need to be prioritised sooner if it becomes exhausted because of increased CO_2 production).
    d. Maintain anaesthesia with intravenous agents.
2. Dantrolene:
    a. Dantrolene acts on the EC coupling mechanism to reduce the accumulation of calcium ions within the muscle cells.
    b. The starting dose of dantrolene is 2.5 mg/kg.
    c. Each 20 mg vial of dantrolene needs to be dissolved by vigorous mixing with 60 mL of water for injection – this is time consuming. Adult patients will require multiple vials for the starting dose (e.g., 10 vials for a patient of 80 kg). At least one person should be assigned the responsibility of continuously preparing the drug.

d. Further doses of 1 mg/kg should be given every 5 min until the metabolic signs i.e. tachycardia, hypercapnoea and hyperthermia are resolving (pause dantrolene and observe when $ETCO_2$ < 6 kPa and core temperature < 38.5 ºC).

e. Recrudescence of the hypermetabolic reaction can occur for up to 14 hr after initial resolution.

f. In the context of an acute MH reaction there is no upper maximum dose limit for dantrolene, although if there is no response after 10 mg/kg the outcome is unlikely to be good (or the presumptive diagnosis of MH should be reviewed).

g. All anaesthetic departments should have an action plan agreed with pharmacy to ensure adequate supplies of dantrolene can be sourced in the event of an MH reaction (see www.ukmhr.ac.uk).

3. Hyperthermia:

    a. Switch off active warming devices.

    b. Active cooling measures should be proportionate to the increase in core body temperature and can range from simply exposing the patient to cardiopulmonary bypass (table of cooling methods).

    c. If the core body temperature exceeds 39 ºC, aggressive cooling should be instituted. These should be stopped once the temperature falls below 38.5 ºC to avoid hypothermic over-shoot.

    d. If the patient has not responded to dantrolene, there is animal evidence that moderate hypothermia (34.5 ºC) may antagonise the MH reaction.

4. Monitoring and sampling:

    a. Continue routine anaesthetic monitoring (SaO_2, ECG, NIBP, and $ETCO_2$).

    b. Establish additional intravenous access with wide bore cannulas.

    c. Insert a central venous catheter to enable drug administration and guide fluid management.

    d. An arterial line should be established.

e. Take blood samples for measurement of K^+, creatine kinase, arterial blood gases, glucose, renal function, hepatic function and coagulation.

f. A bladder catheter should be inserted for measurement of urine output.

5. Hyperkalaemia: the options are:

   a. Insulin. 10 IU insulin in 50 ml 50% dextrose over 5 minutes. The European MH Group guideline suggests 50 IU of insulin in 50 ml 50% dextrose as hyperkalaemia may be profound: with this regimen hypoglycaemia should be anticipated;

   b. $CaCl_2$: 0.1 mmol/kg iv. This is a temporising measure if hyperkalaemia is considered imminently life-threatening. There is experimental evidence that extracellular calcium ions may sustain the skeletal muscle cell calcium overload in MH.

   c. Haemofiltration. This may be necessary in the presence of massive rhabdomyolysis.

6. Acidosis:

   a. Hyperventilate to correct respiratory acidosis.

   b. Sodium bicarbonate can be administered intravenously if pH falls below 7.2.

7. Arrhythmias:

   a. Amiodarone (5 mg/kg), or beta-blockers (esmolol or metoprolol) can be used for tachycardia.

   b. Cardiac arrest should be managed as per ALS guidelines.

   c. Calcium channel blockers should be avoided as they may cause severe myocardial depression in combination with dantrolene.

8. Acute kidney injury: An MH reaction predisposes to an acute kidney injury secondary to the effects of free myoglobin on the kidneys. Myoglobin causes renal damage both by precipitation in the renal tubules and by stimulating lipid peroxidation.

a. A diuresis of 2 mL/kg/h should be established primarily with intravenous fluid. Dantrolene contains mannitol which will help in maintaining an adequate urine output. If an adequate diuresis is not maintained in the presence of rhabdomyolysis furosemide (0.5 - 1 mg/kg) should be given.

b. Alkalinisation of the urine reduces tubular precipitation of myoglobin and lipid peroxidation. There is some clinical evidence to suggest benefit of urine alkalinisation in rhabdomyolysis and no evidence of harm.

c. Data from an animal model of rhabdomyolysis suggests that therapeutic doses of paracetamol reduce renal lipid peroxidation and kidney injury.

9. Disseminated intravascular coagulation. In MH this manifests as a consumptive coagulopathy. Pragmatic administration of platelets and clotting factors is indicated but the coagulopathy is likely to continue until hyperthermia is corrected.

10. The patient should be monitored for a minimum of 24 hours in a critical care environment after the signs and symptoms of MH are controlled. The patient would need to be observed for acute kidney injury, compartment syndrome and recrudescence of the hypermetabolic condition.

Patient counselling and referral:

If MH is considered a possibility in any patient, the diagnosis should be confirmed or refuted. In the meantime, the patient should be informed that they, and their blood relatives, should be treated as at risk of developing MH under anaesthesia until proven otherwise.

It is the responsibility of the proband's named consultant anaesthetist to refer their patient to the relevant specialist MH centre. The UK centre can be contacted at the authors' address and details of other centres, except those in North America and Japan, can be found at www.emhg.org. Details of MH centres in North America can be found at www.mhaus.org/testing/centers. The referring anaesthetist should

provide a narrative account of the reaction and copies of preoperative assessment notes, all anaesthetic charts, post-operative care unit records, results of all investigations (all preoperative investigations, serial CK concentrations, arterial blood gases, electrolytes, liver function tests, etc.). Details of the patient's general practitioner should be sent along with the referral.

Once the referral is received at the unit, a decision will be made regarding the need for further testing. The final decision will be communicated to the referring anaesthetist, general practitioner and the patient.

Confirmation of diagnosis

An updated comprehensive guideline for the diagnosis of MH susceptibility was published in 2015 by the European MH Group[9]. In vitro contracture testing (IVCT) using freshly excised muscle biopsy specimens remains the only definitive means of demonstrating that an individual is **not** susceptible to MH. Recent advances in DNA sequencing technology have meant that initial DNA screening can cost-effectively confirm MH susceptibility with a sensitivity of approximately 40%, thus avoiding the need for muscle biopsy in some probands.

Muscle Biopsy:

The IVCT is performed at specialist centres to ensure quality control and reproducibility of this unique diagnostic procedure. The patients have to travel to the specialist centre for the biopsy because the tests are done on fresh muscle. Muscle specimens (20-30 x 3-5 x 2-3 mm) are dissected at open biopsy from the vastus muscle under local anaesthetic block and are transported immediately to the lab in Krebs' solution: they remain viable for up to 5 hr. The muscle specimens are exposed to increasing concentrations of halothane or caffeine. Susceptible muscle develops a contracture (sustained contraction) at lower concentrations of halothane and caffeine than non-susceptible muscle (Fig. 2). The patients are informed of the results of the IVCT on the same day.

Figure 2 near here

Additional muscle specimens are sent for histopathological examination to exclude any underlying muscle disease that may be associated with a non-specific abnormal IVCT response. Histochemical analysis will also reveal the presence of cores (areas with absence of oxidative enzyme staining) that may indicate the presence of a core myopathy associated with MH susceptibility. Patients with a core myopathy may have such subtle degrees of muscle weakness that they did not appreciate they had an abnormality. They may benefit from neurological referral and, if they are considering starting a family, genetic counselling.

In the UK we do not do the IVCT on children under 10 years of age because we have not demonstrated that the test is fully sensitive below this age. We also require a child to weigh more than 30 kg for them to be tested to allow them to attain sufficient muscle mass.

Genetic testing for Malignant Hyperthermia.

As with many apparently “classical” Mendelian autosomal dominant traits, the genetics of MH has proved more complex than originally thought. Not only is there involvement of multiple genes (RYR1, CACNA1S and others yet unknown) and multiple variants within these genes but there is also consistent evidence that at least a minority of families harbour more than one genetic variant contributing to the MH susceptibility. It is for these reasons that genetic testing cannot exclude MH susceptibility. The role of genetic testing is illustrated in Fig 3.

Figure 3 near here

Conclusion

Knowledge of the pathophysiology of MH aids understanding of its clinical features, which in turn should lead to prompt diagnosis and successful treatment. Activated

charcoal filters are a recent introduction that will aid elimination of the triggering anaesthetic but the key to prevention of mortality and morbidity is administration of dantrolene. Patient counselling and referral for diagnosis and family follow-up is the responsibility of the named anaesthetic consultant.

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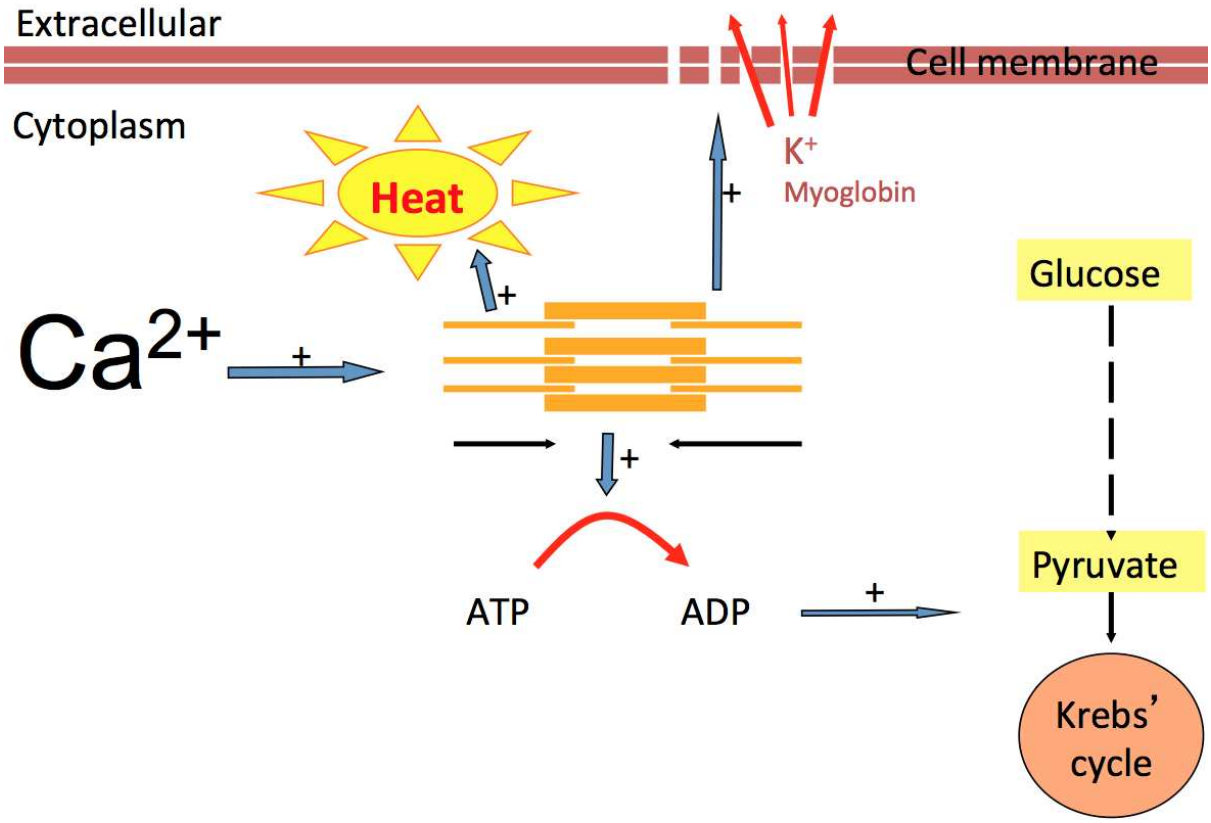
Legends to figures.

Figure 1: Pathophysiology of malignant hyperthermia. The effects of increased skeletal muscle cell calcium ion concentration.

Figure 2: Halothane contracture test. The muscle is stimulated electrically throughout the test and the electrically evoked twitches (thin vertical lines) indicate muscle viability. The thick blue line indicates the baseline tension of the muscle. The muscle is initially stretched to its physiological length (increase in baseline tension) and maintained at this length (decline in baseline tension). Thereafter, any increase in baseline tension is defined as a contracture. a) In a normal individual as exposure of the muscle to halothane is increased from 0.5 to 2.0%, the baseline tension tends to decrease further. b) On the other hand in a susceptible patient a concentration-dependent contracture develops in the presence of halothane.

Figure 3. Diagnostic pathway for investigation of MH susceptibility[9]
MH – Malignant Hyperthermia
IVCT: In vitro contracture testing
MHN – Not susceptible to Malignant Hyperthermia
MHS_{hc}, MHS_{h}, MHS_{c} – Susceptible to Malignant Hyperthermia

Figure 1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Cytoplasm
Heat
K+
Myoglobin
Ca2+
Glucose
Pyruvate
ATP
ADP
Krebs' cycle

Figure 2

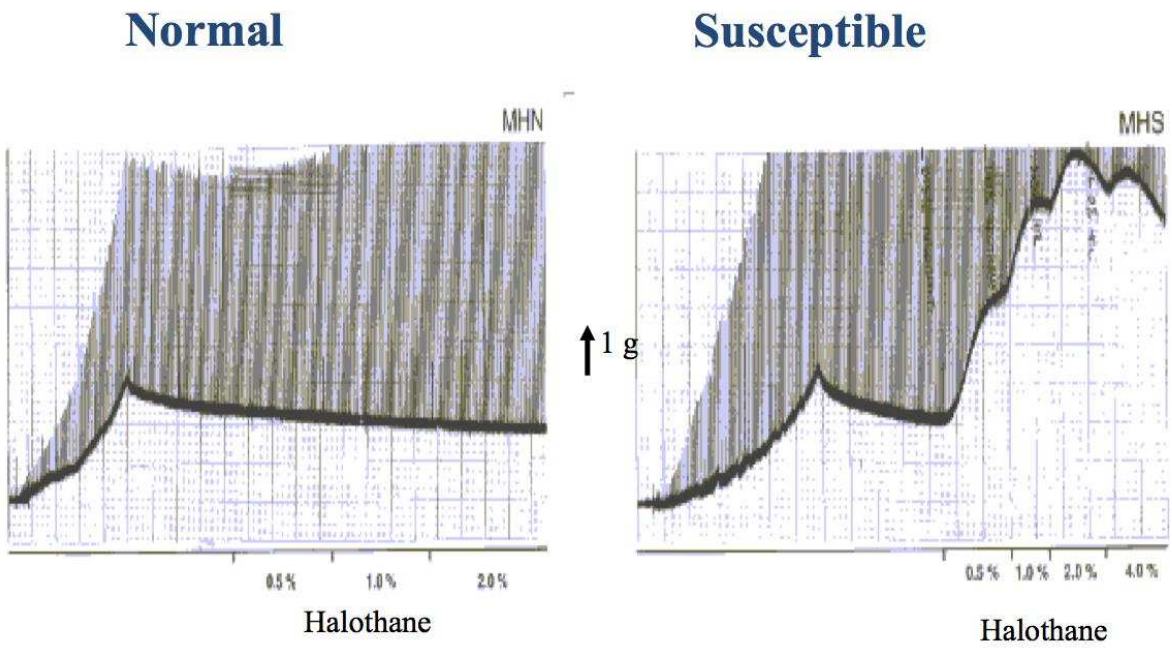
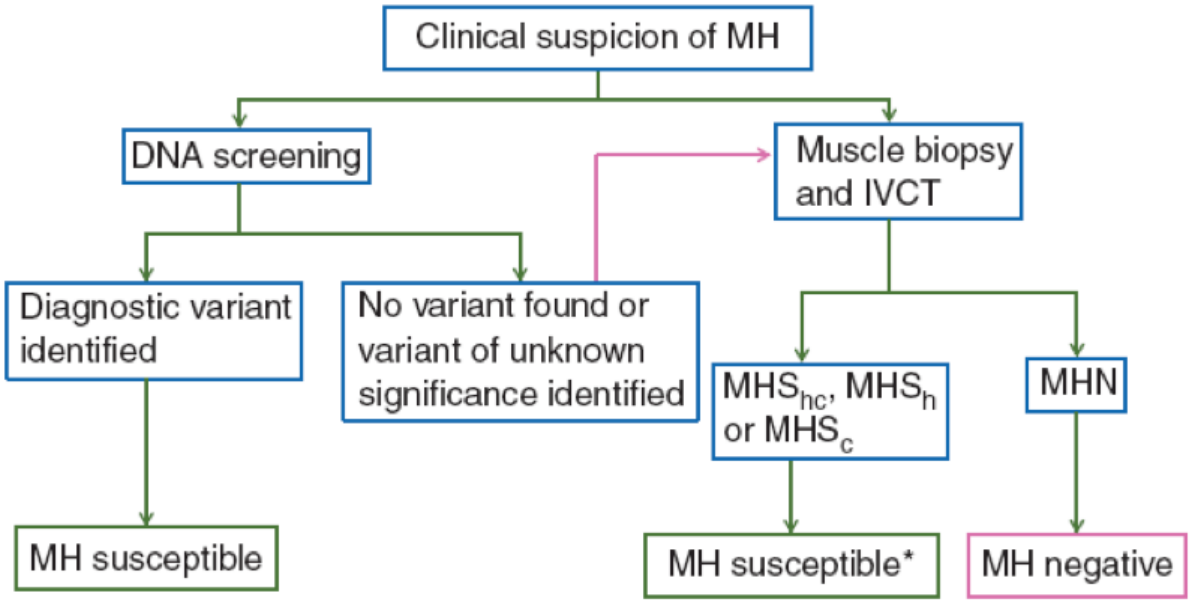

Normal
Susceptible
MHN
MHS
1 g
0.5 %
1.0 %
2.0 %
4.0 %
Halothane
Halothane

Figure 3


Clinical suspicion of MH
DNA screening
Muscle biopsy and IVCT
Diagnostic variant identified
No variant found or variant of unknown significance identified
MHS$_{hc}$, MHS$_{h}$ or MHS$_{c}$
MHN
MH susceptible
MH susceptible*
MH negative