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CLINICAL PRESENTATION OF MALIGNANT HYPERTHERMIA

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As is the case with many medical disorders, malignant hyperthermia (MH) was first described in its most obvious dramatic form. This occurred in 1961, when Denborough and Lovell reported what we later learned was MH, in a young Australian undergoing routine surgery [7]. Over the course of the ensuing quarter of a century, many variations of MH have been described and we are still learning of variants of this syndrome. Even now, there is debate and disagreement as to the presentation of MH in humans [16]. In this article I will discuss the classic presentation of MH and some of the many variants of the syndrome.

Although the clinical manifestations of MH may be a cause for debate, the underlying pathophysiology is clearer. The work of Lopez and colleagues [22] indicates that the hypermetabolism of MH is related to increased intracellular calcium ion concentration; the cause of the release of calcium into the cell is not understood.

MH can be thought of as a spectrum of disorders, ranging from the "classic" case to those with unusual presentations and mild symptomatology. It would be expected, therefore, that the mortality and morbidity from MH would vary, depending on how rapidly the syndrome is diagnosed and treatment begun, and also on the inherent variability of the syndrome itself. The mortality from the most fulminant forms of MH is believed to be 10–15% [26], whereas mortality from other variants may be considerably less.

Also of importance in the manifestation of MH is the effect of concomitant drug administration and environmental factors. For example, it is recognized that non-depolarizing neuromuscular blocking drugs [20] and barbiturates can delay the onset of MH in susceptible swine.

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The acuity of MH also depends on the concentration of the anaesthetic used. Clinical symptoms and signs are less severe in animals receiving 1% halothane than in animals receiving higher concentrations of the anaesthetic [1].

Environmental factors may affect the progression of MH. For example, it has been shown that progression and manifestations are more dramatic after animals are exercised [2, 35]. Increased body temperatures as a result of either environmental factors or perhaps intercurrent infection, may also aggravate the progression of the disorder [15].

Age may also affect the manifestations of MH. It has repeatedly been shown that the incidence of MH is higher in the paediatric and in the young adult populations than in the middle age and older adult population [26].

CLASSIC MALIGNANT HYPERTHERMIA

Those patients having some combination of the following characteristics are "classic" examples of the syndrome:

(1) High body temperatures (greater than 41 °C).
(2) Marked skeletal muscle rigidity.
(3) Metabolic and respiratory acidosis, frequently with base deficit of greater than 10 mmol.
(4) Myocardial changes, usually manifested as arrhythmia.
(5) Marked hyperkalaemia.
(6) Muscle breakdown as manifest by gross increases in serum creatine kinase (CK) concentration to greater than 20000 iu litre^{-1}, together with myoglobinuria.
(7) Family history of MH.

A variety of other changes may occur, including hypercalcaemia and disseminated intravascular coagulopathy (DIC), which is a leading cause of death in fulminant MH [15].

Patients with fulminant MH may have a paradoxical response to suxamethonium. In susceptible swine, suxamethonium in conjunction with

halothane invariably precipitates fulminant MH [18]. However, in humans, fulminant MH may occur despite a normal response to suxamethonium.

Laboratory evaluation of MH usually reveals significant lactic acidosis and increased oxygen consumption and carbon dioxide production.

Arterial P_{CO_2} does not always adequately reflect severity. In a recent study, Gronert and co-workers [17], showed that arterial P_{CO_2} was significantly less than venous P_{CO_2} and suggested that femoral venous blood-gases are more helpful in assessing the severity of the MH episode than are arterial blood-gases.

Fortunately, probably less than 10% of all cases of MH progress to the fulminant variety. Ørding's study [26] of MH in Denmark over the period 1978–1984 revealed that only 6.5% of cases of MH were fulminant.

Recrudescence is another characteristic. Fletcher and co-workers [12] have described a patient with MH in whom metabolic symptoms lasted for several days. In the management of fulminant MH, it may be necessary to continue dantrolene into the early postoperative period and to assess the level of muscle destruction by frequent determination of CK. (CK will peak at 12–24 h after the episode of muscle destruction.) Massive amounts of dantrolene may be necessary to manage patients with fulminant MH, up to and exceeding the recommended 10 mg kg^{-1}. If managed well, the outcome is successful and neurological deficits should not be expected.

Biopsied skeletal muscle will show the classic changes of halothane-induced contracture as well as caffeine contracture at caffeine 2 mmol $litre^{-1}$ or less [30] (see Ørding in this issue, p. 287).

Masseter muscle rigidity with suxamethonium

Muscle rigidity affecting the jaw muscles, particularly after an intubating dose of suxamethonium, is probably the most common manifestation of MH [28], especially in children. A negative history is obtained and the child anaesthetized with halothane or similar inhalation agents by mask. Suxamethonium is then given and trismus noted. In some patients muscle rigidity affecting other muscle groups is recognized. This muscle rigidity may last for 1–3 min and will then usually resolve. If the anaesthetic is continued, MH may develop within minutes, or may take several hours to appear [10].

The clinical characteristics of patients who have had suxamethonium induced muscle rigidity are [8,28]:

(1) Suxamethonium used for intubation.

(2) Although halothane is commonly used for induction of anaesthesia, cases have been reported with ultrashort acting barbiturates.

(3) Usually children aged between 4 and 15 yr are affected. Patients in their 20s and early 30s also exhibit masseter muscle rigidity.

(4) Temperature increases are generally not marked, nor are significant arrhythmias noted. The muscle rigidity lasts for approximately 2–3 min and has been termed a "myotonic" reaction to suxamethonium, since a similar response is seen in patients with myotonic disorders [8].

(5) A family history of MH is generally not found.

Several studies have shown that the coincidence of masseter rigidity with muscle biopsy proven MH is in the order of 50% [8,13,28].

Ørding [26] found that 1 in 12000 patients who receive general anaesthesia and suxamethonium experience masseter muscle rigidity. A provocative retrospective study of masseter rigidity was carried out at the Boston Children's Hospital [31]. Approximately 1% of all children who received halothane and suxamethonium developed masseter muscle rigidity. Two of the 15 patients who developed such masseter rigidity had received suxamethonium previously without apparent problems. Of the records surveyed, 46% of the children who had masseter muscle rigidity were between the ages of 8 and 10 yr, but only 11% of all children undergoing surgery were in this age group.

Our recent studies have also found that masseter muscle rigidity was more common in children. The average age of patients referred for biopsy who had experienced masseter rigidity was approximately 10 years of age. We found neither gender predisposition for masseter rigidity, nor that it was associated with any particular operative procedure. Neither muscle histology nor EMG studies were able to distinguish those patients who are MH positive by halothane–caffeine testing from those who are MH negative.

If dantrolene is not administered after the episode of masseter rigidity, increased serum CK concentration will occur, along with a transient episode of myoglobinuria. Therefore, vigorous hydration and diuresis should be assured in the early postoperative period. If the perioperative CK concentration is greater than 20000 (upper

limit of normal 200 iu litre^{-1}), then the likelihood of the patient being susceptible on muscle biopsy is extremely high, if there is no concomitant myopathy. Six of the 21 patients who experienced masseter rigidity and had serum CK concentrations greater than 20000 iu litre^{-1} were MH positive by muscle biopsy. The chance of the patient being MH susceptible if the serum CK value was greater than 15000 was 88%, and 82% if the CK concentration was greater than 10000 iu litre^{-1} (in the absence of other myopathies). Although some have continued anaesthesia with non-triggering agents after an episode of masseter rigidity, this can only be condoned if dantrolene is readily available and end-tidal carbon dioxide monitoring is undertaken. In any event, patients who have experienced masseter rigidity should be evaluated by a neurologist and, if possible, by muscle biopsy, since, occasionally, an underlying myopathy will be found. All patients who have myoglobinuria after anaesthesia should have a diagnostic muscle biopsy performed.

Prompt recognition of masseter rigidity and discontinuation of the anaesthetic is usually not associated with further progression to fulminant MH. Dantrolene may prevent the increase in serum CK concentration and myoglobinuria after operation and should, therefore, be administered soon after the episode of masseter rigidity.

The differential diagnosis of masseter muscle rigidity is limited. Apart from an inadequate dose of suxamethonium or underlying dystrophia myotonica or myotonia congenita, MH must be considered. Myotonic states can usually be diagnosed by clinical history and EMG.

What, then, can be said of the patient who experiences masseter muscle rigidity and who is MH negative by muscle biopsy testing, but also has had a transient increase in CK concentration? The patient should be advised to avoid receiving suxamethonium. Since suxamethonium-induced masseter rigidity has not been reported to be inherited, we have chosen not to biopsy family members of patients who experienced masseter rigidity but are MH negative by halothane and caffeine contracture testing.

A special problem is the discordance in incidence of muscle masseter rigidity and the incidence of MH. Even if 50% of all patients experiencing muscle rigidity were MH susceptible according to the data of Schwartz and colleagues [31], the overall incidence of masseter rigidity in children would be 1 in 200 cases. Clearly fulminant MH is not that frequent. Perhaps the underlying propensity to developing MH is much commoner in the population than we have imagined, and age affects the manifestations of MH such that, as we grow older, the ease of triggering the syndrome decreases. Further studies on masseter muscle rigidity, both epidemiological and pharmacological, are essential in order to guide the clinical management of postoperative MH.

Uncommonly, MH may present in the recovery room. The patient usually has had a normal anaesthetic course but, after operation, develops tachycardia, fever and classic signs of MH. In our studies of postoperative fever, we have found that fewer than 20% of patients will be MH susceptible on muscle biopsy. These data, of course, are derived from a selective population referred to a biopsy centre for evaluation. This is an especially perplexing problem, since postoperative fevers are not uncommon. Again, the extent of the increase in temperature, the presence of increased concentrations of CK and lack of underlying infection, will be the indications for diagnostic muscle biopsy.

MALIGNANT HYPERTHERMIA AND MYOPATHIES

Several myopathies have been associated with MH. The most well established association is between *Central Core Disease* and MH [14]. Muscle rigidity as well as fulminant MH have been described in patients with this condition [10].

Another uncommon myopathy associated with MH is the *King Syndrome* [23]. The typical features are cryptorchidism, pectus carinatum, low set ears, webbed neck and the development of kyphoscoliosis at an early age. Only a few cases of King Syndrome have been reported in association with MH. The usual clinical manifestations are fever and tachycardia, and other symptoms and signs indistinguishable from classic MH.

Patients suffering from *Duchenne muscular dystrophy* frequently have a most unusual presentation of MH [29]. Typically, after an uneventful anaesthetic with a triggering agent such as halothane, with or without suxamethonium, the patient exhibits a ventricular arrhythmia and cardiac arrest occurs in the recovery room in association with marked hyperkalemia and significant acidosis [21]. If the patient has received suxamethonium, marked myoglobinuria may become manifest.

It has long been known that patients suffering from *osteogenesis imperfecta* will display increased temperature during operation [27]. Several cases of classic MH have been described in osteogenesis imperfecta patients. We have biopsied five individuals with osteogenesis imperfecta and only one has been MH susceptible.

A few cases of MH have been described with other disorders, but since these are single case reports, no picture of a typical presentation emerges. Among these disorders are myotonia congenita, Schwartz–Jampal Syndrome, and hyperkalaemic periodic paralysis. Arthrogryposis multiplex has occasionally been thought to be associated with MH, but a recent report has failed to show an association [3].

MALIGNANT HYPERTHERMIA OUTSIDE THE OPERATING ROOM

In some swine breeds, MH can occur in the absence of pharmacological trigger agents. Susceptible pigs will develop signs and symptoms of classic MH initiated by stress, fighting, and even during mating [25]. Fortunately, this is not the case in humans. Anecdotal reports of sudden death among suceptible patients have been looked upon with scepticism, since many of the circumstances surrounding the deaths, and the family pedigrees, have not been thoroughly described in scientific terms [36]. If MH susceptible patients are more prone to sudden death, this is extremely rare. A single documented case of *episodic fever* relieved by dantrolene in a biopsy-proven susceptible patient has, however, been described [19]. More recently, two patients who experienced environmentally induced heat prostration were MH susceptible on halothane and caffeine contracture testing [11]. However, there are insufficient data to indicate if all susceptible subjects have a greater likelihood of suffering heat related syndromes in extreme environmental temperatures.

Sudden Infant Death Syndrome (SIDS), is a disorder that probably has multiple aetiologies, including airway abnormalities, undiagnosed congenital lesions and metabolic defects [33]. Of 15 families in which there was a history of SIDS, five parents were MH susceptible on halothane contracture testing [6]. In an epidemiological study, Ellis and co-workers have not been able to confirm a higher coincidence of SIDS in MH suceptibles [9].

The *Neuroleptic Malignant Syndrome* (NMS), is a syndrome characterized by increased temperature, muscle rigidity, acidosis, and autonomic disturbances which respond to dantrolene therapy [4]. However, the time course of this syndrome is hours to days, in contrast to MH, in which it is minutes. NMS is triggered by such psychoactive agents as haloperidol and phenothiazines. Of seven patients we have biopsied who suffered clinical NMS, five showed contractures typical for MH on halothane challenge [5]. However, others have not found typical contracture changes in patients biopsied for NMS. Other differences between MH and NMS are striking. For example, the butyrophenone droperidol is not a trigger for MH, but haloperidol apparently is for NMS. Many believe that NMS results from pharmacological blockade of dopamine receptors. Indeed, the dopamine agonist, bromocriptine, is a useful adjunct in the therapy of NMS. Another difference is the absence of a reported case of NMS in an MH patient or *vice versa*. Some NMS patients have even received suxamethonium for electroshock therapy without problems. NMS, however, is of special significance because it is estimated that 1.5% of all patients receiving psychoactive drugs will experience this syndrome with an approximate 20% mortality rate [32]. Until further clarification is available, it is prudent to treat NMS patients as if they were MH susceptible.

CONDITIONS THAT MIMIC MALIGNANT HYPERTHERMIA

Since fever, tachycardia and tachypnoea are relatively non-specific signs and symptoms, it might be expected that a variety of conditions will mimic MH.

Tachycardia and temperature increase are changes seen regularly in patients with sepsis.

Not uncommonly, small children are thoroughly covered during anaesthesia and are given humidified gases in order to prevent heat loss. In some cases, this may lead to increased temperature because of failure to dissipate endogenous heat.

Perhaps the most common cause of tachycardia and tachypnoea during anaesthesia is stimulation during light planes of anaesthesia.

Thyrotoxicosis marked by temperature increase, tachycardia, and hypertension is often difficult to distinguish from MH [34].

As mentioned earlier, rigidity with suxamethonium is the hallmark of not only MH, but also myotonias [24].

Phaeochromocytoma has many clinical signs and symptoms similar to MH. Tachycardia, hypertension and even hyperthermia may occur during an acute episode of phaeochromocytoma.

A rather unusual cause of increased temperature, along with hyperactive muscle activity, tachycardia and death, is the inadvertent injection of water soluble radiological contrast agents to the cerebrospinal fluid.

Not infrequently, hypoxic brain damage leads to postoperative temperature instability and convulsions, which are often attributed to MH. Most typically, the intraoperative course is marked by tachycardia and then precipitous bradycardia in association with "dark blood" (classic signs of hypoxia, usually the result of the delivery of hypoxic mixtures of gases or misplacement of a tracheal tube). Following cardiopulmonary resuscitation, the patient fails to awaken. Within 2 h, increase in temperature, posturing and convulsions occur, along with mildly increased serum CK concentrations (1000–5000 iu litre^{-1}). The patient either remains in a vegetative state or is markedly brain damaged. The diagnosis of MH is thus invoked to explain the temperature increase as well as the apparent muscle rigidity. In reality, however, these changes are the result of central nervous system damage, particularly affecting the hypothalamus.

CONCLUSION

Classic MH is the most dramatic and deadly manifestation of a syndrome that has many variants of presentation. Our current problem is to explain scientifically these variant presentations. They may all result from the same basic underlying pathophysiology, or may arise from several different intracellular derangements, all resulting in a final common pathway of increased intracellular ionic calcium and hypermetabolism.

Crucial signs that should alert the anaesthetist first to diagnose and then to treat MH are:

(1) Muscle rigidity after suxamethonium.

(2) Precipitous increase in end-tidal carbon dioxide concentration in the absence of a change in minute ventilation.

(3) Unexplained hypertension and tachycardia, especially with deep planes of anaesthesia.

(4) Unexplained myoglobinuria in the postoperative period.

(5) Unexplained marked increase in body temperature in the perioperative period.

It is apparent that, with the widespread acceptance of end-tidal carbon dioxide monitoring and mass spectrometry, MH is being detected earlier, and appropriate treatment instituted more promptly. Through such early recognition, and treatment with dantrolene, we can reasonably expect a further decrease in the mortality and morbidity of this enigmatic disorder.

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