Malignant hyperpyrexia

Malignant hyperpyrexia, as its name suggests, is a condition characterised by a potentially fatal rise in body temperature which occurs during certain types of anaesthesia in genetically susceptible individuals. The rise in body core temperature may be at an alarming rate of greater than 5°C per hour and indicates the presence of an appreciable and inappropriate metabolic stimulation. If left untreated the temperature will rise progressively towards 43 to 45°C at which death occurs. The pyrexia is accompanied by a tachycardia, a progressive rise in oxygen consumption with cyanosis, and a rise in CO₂ production with respiratory acidosis.

A second feature of malignant hyperpyrexia is muscle spasm which may occur in response to suxamethonium given at induction of anaesthesia or which may develop slowly in response to halothane or any of the other inhalational anaesthetic vapours including diethyl ether, chloroform, and ethrane. Muscle tissue in spasm liberates potassium causing a noticeable hyperkalaemia which may prove fatal, releases creatine kinase which may reach astronomical values, and myoglobin which can induce renal failure due to tubular obstruction. Severe metabolic acidosis is due to lacticacidaemia; shortly before death arterial pH often falls below pH 7.0.

Other acute features include a consumptive coagulopathy with diffuse bleeding from wounds and into mucous membranes.

Types of presentation

Malignant hyperpyrexia occurs in three forms:

- (a) The fulminant and classical syndrome described above still occurs though it represents a failure of diagnosis and adequate treatment.
- (b) An aborted form is now more commonly reported in which one or more of the signs have been identified and the anaesthetic (and also surgery) is terminated prematurely with or without specific treatment.
- (c) Missed cases of malignant hyperpyrexia have clearly occurred and will continue to occur. In the first family in which this disorder was described by Denborough and Lovell¹ there had been 10 missed and fatal cases. Anaesthetic disasters, even of recent times, are often unearthed in malignant hyperpyrexia families under investigation.

Incidence

While malignant hyperpyrexia must be considered

an uncommon condition with an incidence of around 1:50 000 of the anaesthetised population, it is far from rare. As over four million anaesthetics are administered annually in the United Kingdom, 80 cases occur each year. With a mortality of 20 to 40% malignant hyperpyrexia must be one of the commonest causes of death in the seemingly fit anaesthetised subject.

The incidence in children is greater than in adults,² due perhaps to the common use of 'trigger' agents during anaesthesia in this age group and perhaps also to the relative instability of metabolic processes.

Treatment

General management. As soon as a provisional diagnosis of malignant hyperpyrexia is made, anaesthesia and surgery should be terminated if possible, or continued without using trigger agents. Body temperature, blood gases and serum potassium should be measured repeatedly and acidosis and hyperkalaemia treated as necessary. A forced diuresis helps to prevent renal failure. Electrocardiographic monitoring can warn of the rapid development of hyperkalaemia, which may be especially notable and uncontrollable in children. If serum potassium begins to rise it is wise to alert the dialysis team, as the potassium concentration may not respond to insulin or ion exchange treatment.

Specific management. The drug of choice to reverse malignant hyperpyrexia is dantrolene, a hydantoin derivative. Dantrolene acts by reducing the sarcoplasmic ionised calcium concentration by either an effect on the sarcolemma or on the sarcoplasmic reticulum. High doses of glucocorticoids are helpful as they are positively inotropic, induce peripheral vasodilatation, and stabilise membranes.

Inheritance

Predisposition to malignant hyperpyrexia is inherited as a single gene, dominant characteristic—the so called malignant hyperpyrexia susceptible state. When serum creatine kinase was used to phenotype members of families with malignant hyperpyrexia the results were so unpredictable that the inheritance pattern seemed to be both variably penetrant and variably expressive. With muscle testing the mode of inheritance has become clearer.

For the disease to be expressed three conditions need to be satisfied. Firstly the presence of the

malignant hyperpyrexia susceptible state, secondly exposure to trigger agents for a long enough period, and thirdly the presence of an ill defined factor possibly related to stress of either physical or psychological origin. Malignant hyperpyrexia probands have often been found to have had previous anaesthetics with trigger drugs uneventfully when it is assumed the stress factor has been absent.³

Family screening

Once the diagnosis has been confirmed in the proband or in one of the proband's parents, other members of the family should be screened. The family members to be screened should have a 50% chance of inheriting the malignant hyperpyrexia susceptible state—this includes parents, siblings, and children of a confirmed subject. Results in children are unreliable until 10 years of age.

The screening procedure involves a muscle biopsy of one of the vasti muscles followed by in vitro exposure of the living muscle to caffeine⁴ and halothane.⁵ Latterly a test protocol and criteria for diagnosis have been agreed by the newly established European Malignant Hyperpyrexia Group.⁶

Anaesthesia for malignant hyperpyrexia susceptible patients

The vast majority of drugs used in anaesthesia are quite safe for these patients. Safe anaesthesia can be provided for all types of surgery and investigations providing the anaesthetist is fully aware of the patients' susceptibility.

In this laboratory the muscle biopsy is taken under general anaesthesia using fentanyl, thiopentone, and nitrous oxide via a mask. Diazepam, pancuronium, atracurium, and local anaesthetics (perhaps avoiding lignocaine) are also safe, as are opioids and neostigmine.

Aetiology

Most studies of the aetiology and pathogenesis of malignant hyperpyrexia have been performed in swine. Landrace, Poland China, and Pietrain breeds of swine are often found to be susceptible and the latter breed is particularly reactive. In these animals 'awake triggering' is seen during hot weather and during muscular exertion such as copulation.

The basic defect seems to affect intracellular ionic calcium. The origin of the high calcium concentration is not yet known though three sites have been suggested, namely sarcoplasmic reticulum, mitochondria, and extracellular calcium leaking across the sarcolemma from the extra cellular fluid.

A high intracellular calcium stimulates metabolism and causes muscle spasm. Most of the other signs described are secondary to these two.

Related conditions

Over the past decade malignant hyperpyrexia has been linked with several other diseases, usually in an attempt to explain the aetiology of the possibly related disease. In no case has the relation been proved and when the association has been examined critically evidence for it has been sparse.

(a) Sudden infant death. The report⁷ that one third of parents of SIDS victims show muscle abnormalities consistent with malignant hyperpyrexia susceptibility has not been confirmed. In our own laboratory no malignant hyperpyrexia susceptible parent has yet been identified out of seven family studies. Also, out of 300 malignant hyperpyrexia susceptible families known to us, the incidence of SIDS is not significantly greater than in the general population (Halsall and Ellis unpublished observation).

(b) Heat stroke. Much has been written about awake triggering of malignant hyperpyrexia, especially in relation to heavy exercise such as marathon running during which a proportion of runners develop core pyrexia. Although some of the clinical anecdotes bear similarities, the malignant hyperpyrexia susceptible state has never been confirmed unequivocally by muscle studies.

(c) Muscle diseases. A variety of muscle diseases including myotonia congenita, Duchenne dystrophy, and various myopathies have been linked with malignant hyperpyrexia but the connection has never been proved beyond clinical observations and limited biochemical investigations.

(d) Neuroleptic malignant syndrome. This syndrome is associated with neuroleptic drug treatment and has been recognised by psychiatrists to be a variant of malignant catatonia. Moyes⁸ described a child who died preoperatively after phenothiazine premedication which he described as malignant hyperpyrexia. There is no direct evidence that phenothiazines are dangerous for these individuals, though they should be avoided if neuroleptic malignant syndrome has been suspected.

Further reading

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F R ELLIS
University Department of Anaesthesia,
St James's University Hospital,
Leeds LS9 7TF