MALIGNANT HYPERTHERMIA: A STUDY OF AN AFFECTED FAMILY

D. G. LARARD, C. P. RICE, R. ROBINSON, R. W. SPENCER AND R. A. WESTHEAD

SUMMARY

A case of malignant hyperthermia is described. The possible occurrence of similar susceptibility among members of the patient's family was investigated by measuring their serum creatine phosphokinase activities. Patients who carry the trait have no presenting clinical stigmata and there is no specific screening test to detect its presence. The condition is more common than is generally believed. It is suggested that it would be worthwhile to reassess the diagnosis in patients who have died under anaesthesia from obscure causes, to consider the possibility that some of these may have been cases of malignant hyperthermia, and to study the serum creatine phosphokinase activities of their surviving relatives.

Malignant hyperthermia is a condition characterized by rapidly developing fever and often by skeletal muscle rigidity in association with general anaesthesia. It is genetically determined (Denborough et al., 1962; Davies and Graves, 1966; Purkis et al., 1967; Relton, Creighton and Conn, 1968; Britt and Gordon, 1969; Britt, Locher and Kalow, 1969; Britt and Kalow, 1970b).

Even if susceptibility is suspected, it will not be clinically apparent before anaesthesia is started. At present, the anaesthetic mortality rate from malignant hyperthermia is not less than 60 per cent.

Though relatively few cases of malignant hyperthermia have been reported from Britain, the condition is probably not so rare as is generally assumed. We are aware of six other unpublished cases in the Midlands besides our own which we present here, all but one of which were fatal (Dobson, H. R., Hall-Davies, G., McNeil, W. Townley, and Rikards, J. F., 1970, personal communications).

CASE REPORT

A healthy, well-developed girl of 13 years was admitted for the repair of a blocked tear duct. She had previously received several anaesthetics for minor e.n.t. procedures without suffering any incident worthy of note. Anaesthetic records of her previous operations are, unfortunately, not available, but it is unlikely that she had received either suxamethonium or methoxyflurane, because of the nature of the surgery and the usual methods of anaesthesia current at that time.

The pre-operative examination revealed nothing abnormal. The systolic blood pressure was 110 mm Hg and the pulse rate 80 beats/min. One hour before the operation, the patient was given papaveretum 8 mg and hyoscine 0.4 mg intramuscularly. The response to premedication was normal; the blood pressure and pulse rate remained unchanged.

Induction of anaesthesia was by intravenous thiopentone 250 mg with tubocurarin 2 mg, followed by suxamethonium 50 mg. There was no abnormal reaction to these drugs and intubation was performed easily with an armoured latex endotracheal tube.

Anaesthesia was maintained on a Boyle-Magill circuit with spontaneous ventilation using nitrous oxide (6 L/min) and oxygen (3 L/min) and methoxyflurane reducing from 1.5 to 0.5 per cent. The anaesthesia continued uneventfully with no change in blood pressure or pulse rate until 50 minutes after induction, when it was noticed that the right arm, on which the sphygmomanometer cuff was placed, felt warmer than the rest of the body. Respiration, blood pressure, skin colour and muscle tone remained unchanged, but the pulse rate had risen to 90 beats/min.

Fifteen minutes later, rapidly diminishing respiratory excursions were shortly followed by respiratory and then cardiac arrest. Ventilation with oxygen and closed cardiac massage were immediately begun. At this time the patient felt generally hot and dry. There was severe generalized muscular spasm. Masseter spasm had occluded the endotracheal tube and was relieved with difficulty using a mouth gag. The upper limbs were in tonic flexion and the lower limbs in extension. There was some initial difficulty with cardiac massage due to the rigidity of the thorax. The pupils were normal in size but unreactive to light. There was no fundal change. The rectal temperature was 41°C.

A presumptive diagnosis of malignant hyperthermia was made and cooling started with wet towels, fans and ice. External cardiac massage produced a good circulation. Electrocardiograph monitoring showed asystole. An oesophageal temperature probe showed a maximum temperature of 41°C. An intravenous infusion of 4.2 per cent sodium bicarbonate solution was begun and arterial blood taken for the measurement of electrolytes and blood-gases.

The following drugs were given intravenously: glucose 50 g, hydrocortisone 200 mg, mannitol 25 g, and pan-
curonium (total of 20 mg). Methylprednisolone 4 mg was given intramuscularly. The pancuronium had no effect on the muscular contractions.

Thirty minutes after the arrest, a spontaneous cardiac impulse returned with a grossly abnormal electrocardiograph tracing. The systolic blood pressure, initially 80 mm Hg, rose to 100 mm Hg after 10 minutes. The central venous pressure was +14 cm H₂O and, as only 50 ml of urine had been formed since the arrest, frusemide 40 mg was given but without effect. The body temperature had by now fallen to 36°C and active cooling was stopped.

The results of the arterial blood sample taken immediately after the arrest were Pao₂ 510 mm Hg; Paco₂ 56 mm Hg; pH 6.9; standard bicarbonate 8.5 m.equiv/l; serum potassium 8.3 m.equiv/l. Glucose, insulin and calcium gluconate were given to counteract the hyperkalaemia; further sodium bicarbonate was given and a lignocaine infusion begun. A subsequent arterial blood sample showed the following results: Pao₂ 600 mm Hg; Paco₂ 46 mm Hg; pH 7.42; and standard bicarbonate 27 m.equiv/l.

One hour later, cardiac arrest occurred in asystole.

From this time until resuscitation was discontinued, various resuscitative measures were attempted, including adrenaline intravenously and by intracardiac injection, intravenous isoprenaline and the insertion of an internal cardiac pacemaker. Asystole continued, however, and resuscitation was abandoned.

Family history.

It was later learned that the patient’s brother, at the age of 5 years, had died under general anaesthesia 6 years earlier. Death had been attributed to “anoxia and aspiration of the gastric contents” but, in retrospect, certain features suggest that he too almost certainly died from malignant hyperthermia. Anaesthesia had been induced with nitrous oxide, oxygen and halothane. Intravenous suxamethonium was followed by gross generalized muscle spasm, such that intubation was impossible. Further doses of suxamethonium were given but no relaxation was achieved. Forcible intubation was undertaken because of severe hypoxia. Cyanosis continued in spite of ventilation with oxygen, and irreversible cardiac arrest occurred 30 minutes after induction. The body temperature was not measured. For the rest of this discussion it is assumed that this child died due to malignant hyperthermia.

METHODS AND RESULTS

Skeletal muscle contains large amounts of the enzyme creatine phosphokinase (c.p.k.). In patients with certain myopathies, the serum activity of this enzyme is abnormally high. Isaacs and Barlow (1970) suggested that patients who suffer from malignant hyperthermia under anaesthesia have a subclinical myopathy and they found that some asymptomatic relatives of the patients had raised serum c.p.k. activities. Their findings suggested that these relatives had inherited the trait.

A raised serum c.p.k. activity may be the only indication that an individual could suffer from malignant hyperthermia under anaesthesia. It seemed worthwhile, therefore, to estimate the serum c.p.k. activities of all the blood relatives of the propositi.

The parents of our patient supplied a family tree going back to the child’s deceased grandparents.

Blood specimens were centrifuged shortly after they were collected, the serum separated, and sent by post to the laboratory. The c.p.k. activities were measured by an automated version of the method of Hughes (1962). Figure 1 illustrates the family tree.

<table>
<thead>
<tr>
<th>Relative</th>
<th>Sex</th>
<th>Serum (c.p.k.) activity (i.u./l.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II 1</td>
<td>M</td>
<td>37.8</td>
</tr>
<tr>
<td>II 2</td>
<td>M</td>
<td>67.9</td>
</tr>
<tr>
<td>II 3</td>
<td>F</td>
<td>115</td>
</tr>
<tr>
<td>II 4</td>
<td>F</td>
<td>71</td>
</tr>
<tr>
<td>II 5</td>
<td>M</td>
<td>397</td>
</tr>
<tr>
<td>II 6</td>
<td>F</td>
<td>41.2</td>
</tr>
<tr>
<td>II 1</td>
<td>F</td>
<td>30.8</td>
</tr>
<tr>
<td>II 2</td>
<td>F</td>
<td>44</td>
</tr>
<tr>
<td>II 4</td>
<td>M</td>
<td>94</td>
</tr>
<tr>
<td>II 5</td>
<td>F</td>
<td>54.8</td>
</tr>
<tr>
<td>II 6</td>
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<td>298</td>
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<tr>
<td>II 10</td>
<td>M</td>
<td>53.5</td>
</tr>
<tr>
<td>II 12</td>
<td>F</td>
<td>41.2</td>
</tr>
</tbody>
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Table I shows the results of the serum c.p.k. determinations. We have expressed the results in figure 1 in terms of (1) normal activity, (2) moderately increased activity (up to one-fifth higher than the upper limit of the conventional “normal range”), and (3) considerably increased activity (2–5 times the upper limit of the “normal range”).

It should be borne in mind that 2-½ per cent of...
normal individuals may have values above the upper limit of the conventional "normal range". However, although the mother of the propositi (II 4) had a serum c.p.k. activity that was only moderately raised, the probability that her result could occur in a normal individual is very low (P < 0.003). It is, therefore, highly unlikely that she is normal, even though her serum c.p.k. activity is not strikingly raised. The serum c.p.k. activity was normal in all those spouses married to members of the family with progeny. All the surviving blood relatives of the husband of II 4 (father of the propositi) had normal serum c.p.k. activities.

**DISCUSSION**

Previous studies have shown that the inheritance of malignant hyperthermia is mediated by an autosomal dominant gene with reduced penetrance and variable expressivity. The history and findings in this family are in accord with this view.

The aetiology of malignant hyperthermia is unknown, though almost certainly it is not a single entity. Clinically, patients can be divided into two groups: those who develop muscle rigidity under anaesthesia, and those who do not. Kalow and associates (1970) showed that the properties of isolated strips of muscle from patients who had recovered from malignant hyperthermia varied. Muscle from patients who had had rigidity showed enhanced sensitivity to caffeine and to the potentiating effect of halothane; muscle from a patient who had not had rigidity reacted normally.

Some susceptible patients survive anaesthesia, but there is no demonstrable clinical or biochemical feature that distinguishes those who survive from those who succumb. It is tempting to postulate that those patients with the higher, and indisputably abnormal serum c.p.k. activities are at the greater risk. However, there is no evidence either for or against this view. Nevertheless, it seemed worthwhile to attempt an approximately quantitative survey of the serum c.p.k. activities of the relatives of the propositi if only as a demonstration of the variable expressivity of this gene.

The survey emphasizes two points: first, that individuals with but moderately raised serum c.p.k. activities—such as the mother of the propositi—may have children destined to die from the disease; and secondly, that parents with normal c.p.k. activities (such as II 2) may nevertheless have children with raised serum c.p.k. activities who presumably may be affected by the disease.

It is interesting to note that relative II 1 was given halothane and suxamethonium at the age of 38 years without recorded untoward effect. Eleven years later his serum c.p.k. activity is normal. It cannot, however, be assumed that successful anaesthesia is any guarantee of future safety.

Britt and Kalow (1970a) have estimated the incidence of malignant hyperthermia as between 1 in 6,800 and 1 in 38,000 of the population. The patients have no presenting clinical stigmata and there is no simple and rapid screening test one could perform on all patients. Serum c.p.k. determinations, though providing a useful warning, are not specific. Raised serum activities may be found in many conditions in which malignant hyperthermia does not develop but these are usually accompanied by some, possibly characteristic, clinical presentation. Usually, the serum activities are very high indeed as, for example, in the preclinical stage of Duchene muscular dystrophy (Pearce, Pennington and Walton, 1964b). Asymptomatic carriers of muscular dystrophy and dystrophia myotonica may have raised serum c.p.k. activities which are of the same order of magnitude as those found in malignant hyperthermia (Pearce, Pennington and Walton, 1964b). Pearce, Pennington and Walton (1964a) found that muscular exercise did not significantly affect serum c.p.k. activities but Griffiths (1966) found raised values in some apparently healthy subjects after normal muscular activity.

Unless a specific diagnostic test is devised, it seems likely that the liability to malignant hyperthermia will remain undetected in most susceptible families until some unfortunate member of the family receives a general anaesthetic which precipitates the condition. Even then, safety will depend on the condition being diagnosed and the family being adequately investigated.

The clinical features of malignant hyperthermia may vary. There may or may not be muscle rigidity. In 21 of 89 cases collected by Britt and Kalow (1970a) rigidity was not recorded. Clinical signs usually present immediately after induction of anaesthesia but may be delayed by an hour or more. In two of the five cases reported by Ryan and Papper (1970) an abnormal response was not noted initially.

It has been suggested that in the rigid form of malignant hyperthermia procaine amide may be of value in relieving both rigidity and fever. Beldavs and colleagues (1971) showed that the slow infusion of a total of 700 mg of procaine amide reversed the skeletal muscle rigidity and this was accompanied by
a fall of temperatures from 112°F to 95°F within 19 minutes.

We suggest that in the absence of an alternative cause, a presumptive diagnosis of malignant hyperthermia should be made whenever a severe hyperthermic response to anaesthesia occurs.

Blood relatives of the patient should be studied by measuring their serum c.p.k. activities, and should not be cleared of suspicion of carrying the trait unless they have all been found to have normal c.p.k. activities. Even so, caution is necessary as the expressivity of the trait is variable and its penetrance may be reduced.

It would be valuable to reassess the diagnosis in patients who have died under anaesthesia from obscure causes, to consider the possibility that some of them may have been cases of malignant hyperthermia, and to investigate the serum c.p.k. activities of their surviving relatives.

REFERENCES


HYPERTERMIA MALIGNE: ETUDE D'UNE FAMILLE AFFECTEE PAR CE TYPE DE TROUBLE

SOMMAIRE

Un cas d'hypertermie maligne est décrit. On a étudié la possibilité de survenue d'une susceptibilité similaire parmi les membres de la famille du malade, en procédant au dosage d'activité de leur phosphokinase créatinique sérique. Les malades porteurs de cette caractéristique ne présentent pas de stigmates cliniques correspondants et il n'existe aucun test de "screening" spécifique permettant de détecter celle-ci. Cette affection s'avère être plus fréquente qu'on le pense généralement. Il est suggéré qu'il vaudrait la peine de revoir le diagnostic avancé pour des malades décédés du fait de causes obscures au cours d'anesthésies, d'envisager la possibilité d'une hypertermie maligne dans certains de ces cas et d'étudier l'activité de la phosphokinase créatinique sérique de leurs parents survivants.

DIE MALIGNE HYPERTHERMIE: EINE UNTERSUCHUNG EINER BETROFFENEN FAMILIE

ZUSAMMENFASSUNG

Es wird ein Fall von maligner Hyperthermie beschrieben. Das mögliche Vorliegen einer gleichen Bereitschaft bei den Familienmitgliedern des Patienten wurde mittels der Bestimmung der Kreatinphosphokinase-Aktivitäten im Serum untersucht. Patienten, die die Anlagung besitzen, weisen keine klinischen Symptome auf, und es gibt keine spezifische Untersuchungsmethode, um diese Veranlagung festzustellen. Die Erkrankung ist häufiger, als allgemein angenommen wird. Es wäre wahrscheinlich lohnenswert, die Diagnose auf Patienten überprüfen, die während der Narkose unter ungeklärten Umständen verstorben sind, an die Möglichkeit zu denken, dass es sich bei einigen von ihnen um Fälle von maligner Hyperthermie gehandelt haben könnte, und die Kreatinphosphokinaseaktivitäten im Serum ihrer noch lebenden Angehörigen zu untersuchen.

HIPERTERMIA MALIGNA: ESTUDIO DE UNA FAMILIA AFECTADA

RESUMEN

Se describe un caso de hipertermia maligna. Fue investigada la posible ocurrencia de una susceptibilidad similar en los miembros de la familia del paciente mediante la medición de las actividades de la creatina fosfocinasa del suero. Los pacientes portadores del carácter no presentan estigmas clínicos ni existe ninguna prueba específica de selección para determinar su presencia. Esta afección es más frecuente de lo que se suele creer. Se sugiere que valdría la pena volver a evaluar el diagnóstico en pacientes que han muerto bajo anestesia por causas obscuras, para considerar la posibilidad de que algunos puedan haber sido casos de hipertermia maligna, y estudiar las actividades de la creatina fosfocinasa de sus parientes aún vivos.