MALIGNANT HYPERPYREXIA

Two Case Reports

BY

R. M. Davies, K. J. Packer, J. Titel and V. Whitmarsh

SUMMARY

Detailed reports are presented of two cases of malignant hyperpyrexia occurring in two males. Both patients died despite early recognition of the syndrome and vigorous treatment.

The term malignant hyperpyrexia has recently come into the vocabulary of anaesthetists following reports (Leading Article, 1968) about patients who have developed a precipitate rise of body temperature during a general anaesthetic, most of whom have subsequently died. The term is associated with an ill defined syndrome, comprising:

(i) A high temperature occurring after the induction of anaesthesia in an apparently fit patient who may have had previous uneventful general anaesthetics.

(ii) A severe metabolic acidosis with associated hyperkalaemia.

(iii) An increase in voluntary muscle tone. This is not a constant finding, nor does it inevitably precede or accompany the rise in body temperature.

We wish to report and discuss two cases which have occurred in our practice in the last year.

CASE REPORT 1.

On February 4, 1968, a general anaesthetic was administered to a 21-year-old Caucasian male for reduction and fixation of his fractured mandible and nose. He had sustained these injuries, but was not knocked out, in an exhibition boxing match 36 hours before operation. Pre-anaesthetic examination revealed a thickset, well-orientated, fit man who had a past history of several nasal boxing injuries, but nothing else of note. He did not smoke, had no allergies, was receiving no drugs, and had had no previous anaesthetics. Examination revealed no abnormal physical signs. His blood pressure was 120/80 mm Hg.

One hour before induction the patient received atropine 0.6 mg i.m. At 11.50 a.m., thiopentone 400 mg and suxamethonium chloride 75 mg (from a single dose vial) were administered via a Gordh needle. However, the patient, though unconscious, was not sufficiently relaxed to tolerate a 10 per cent cocaine nasal spray or permit pulmonary inflation. Further
ventilation was recommenced; occasional abnormal complexes were seen on the e.c.g. The systolic pressure intermittently bizarre. At 1 hour 45 minutes cardiac arrest occurred. Since no palpable pulse resulted from external cardiac compression, at 1 hour 46 minutes after induction, the chest was opened and internal cardiac compression started. An intravenous infusion of saline 0.18 per cent was begun. Venous blood was taken for pH, sugar, and electrolyte estimations. A rectal thermo-couple revealed a temperature higher than 42°C (upper limit of scale). Active cooling measures using wet drapes, ice cubes, and fans were instituted.

Thirty ml of sodium bicarbonate solution (8.4 per cent—table I) and 20 ml 10 per cent calcium gluconate were given over the next 20 minutes. At 25 minutes after arrest (2 hours 10 minutes after induction) adrenaline 1 mg was given into the heart; ventricular fibrillation, but attempts at defibrillation failed to produce a heart beat.

At 2 hours 30 minutes after induction, the rectal temperature was greater than 43.3°C (measured with a mercury thermometer). At this time marked muscular rigidity in the limbs and trunk was first noticed. Two hours 41 minutes after induction (56 minutes after arrest), resuscitation was stopped.

Post-mortem examination revealed no macroscopic evidence of intracranial damage, but enlarged thyroid (50 g), thymus (27 g), and adrenal glands—the latter showed narrowing of the cortices. Micro-thromboemboli were seen in many tissues, including the hypothalamus.

Case report 2.

On July 5, 1968, a general anaesthetic was administered to a 56-year-old Caucasian male for a tooth root extraction; local anaesthesia had been refused. Pre-anesthetic examination revealed a past medical history of a hair-line skull fracture suffered in 1950 without apparent sequelae. His only medication was chlordiazepoxide 10 mg taken daily for "nervousness". He occasionally experienced non-specific muscular aches in his legs. He had no allergies, did not smoke, and had had no previous anaesthetics. His pre-operative blood pressure was 140/70 mm Hg.

One and a half hours before induction levorphanol 1.5 mg, promethazine 25 mg, hyoscine 0.4 mg, and Intracardiac injection of adrenaline again produced tonic muscle contractures free from effect. Rather, the tonic muscle contractures were given to exclude unduly light anaesthesia, but this was without effect. Rather, the tonic muscle contractures increased, causing marked elbow flexion. In addition, the surgeons encountered moderate trismus.

Twenty minutes after induction tachypnoea (40 b.p.m.) developed. The pulse (regular, 64 beats/min) was unchanged, however, and the skin temperature was normal to touch. Five minutes later a rectal thermo-couple revealed a temperature of 37°C. Thirty minutes

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**Table I**

**Case 1. Venous blood biochemistry results.**

<table>
<thead>
<tr>
<th>Time after induction (min)</th>
<th>Bicarb. admin. (m.equiv.)</th>
<th>pH</th>
<th>CO₂ (ml/100 ml) (total)</th>
<th>Cl (m.equiv/L)</th>
<th>K (m.equiv/L)</th>
<th>Na (m.equiv/L)</th>
<th>Blood sugar (mg/100 ml)</th>
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</thead>
<tbody>
<tr>
<td>107</td>
<td>-</td>
<td>-</td>
<td>16.6</td>
<td>98</td>
<td>10.5</td>
<td>155</td>
<td>57</td>
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<tr>
<td>120</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>125</td>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>135</td>
<td>(6.98)</td>
<td>(2.1)</td>
<td>19.2</td>
<td>98</td>
<td>9.3</td>
<td>155</td>
<td>-</td>
</tr>
<tr>
<td>137</td>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>After resuscitation ceased</td>
<td>-</td>
<td>6.79</td>
<td>8.1</td>
<td>98</td>
<td>10.25</td>
<td>140</td>
<td>-</td>
</tr>
</tbody>
</table>

Figures in parentheses = intracardiac sample.
MALIGNANT HYPERPYREXIA

After induction, when the surgical procedure was just completed, the patient's lips appeared cyanosed. One hundred per cent oxygen was substituted for the anaesthetic mixture and the colour quickly improved. The cyanosis did not recur.

Three minutes later the pulse rate had increased (160 beats/min; regular) and the rectal temperature was 38°C. At this time developing hyperpyrexia was suspected, in spite of the nearly normal rectal temperature, because of the sequence of poor muscle relaxation, frank hypertonicity, and tachypnoea. Hydrocortisone 100 mg was injected i.v. Assisted ventilation with 100 per cent oxygen was continued. There was no evidence of returning consciousness. There was intense skin vasoconstriction producing a mottled appearance of the lower limbs.

| TABLE II |
| Mediations administered to Case 1. |
| Intramuscular medication: |
| Atropine sulphate | 0.6 mg |
| Intravenous medications: |
| Sodium thiopentone | 500 mg |
| Suxamethonium | 100 mg |
| Sodium bicarbonate | 30 m.equiv |
| Calcium gluconate | 30 ml 10% solution |
| Intracardiac medication: |
| Adrenaline | 2 mg |
| Intravenous fluids: |
| 1/5 N Saline | 300 ml |

By 57 minutes after induction, the rectal temperature had risen to 39.6°C, and an e.c.g. revealed depressed S-T segments. Total body cooling was begun, using wet drapes, ice, alcohol, and fans. A second 100 mg dose of hydrocortisone was administered. A large intravenous cannula was inserted via a cutdown into the right saphenous vein. The systolic blood pressure was 135 mm Hg. The pulse rate gradually slowed to 56 beats/min.

Sixty minutes after induction, a venous blood sample clotted normally.

At 67 minutes, the rectal temperature was 41.5°C and the oesophageal temperature was higher than 42°C (upper limit of scale). The skin was still mottled and no sweating was evident.

At 71 minutes after induction, chlorpromazine 2 mg was administered i.v. as a peripheral vasodilator to facilitate cooling. The cardiovascular system remained stable and assisted ventilation was continued. The patient was still unconscious.

At 72 minutes a nasogastric tube was inserted and gastric lavage with iced saline was started. Arterial blood was taken for blood gas and electrolyte studies (table III). The rectal and oesophageal temperatures were essentially unchanged in spite of vigorous cooling efforts.

At 77 minutes (20 minutes after the temperature was first elevated) cardiac arrest occurred suddenly. External cardiac compression, intravenous sodium bicarbonate (table III), intravenous lignocaine (table IV), intracardiac adrenaline (0.5 mg × 2), and direct current external defibrillation were successfully applied.

<p>| TABLE III |
| Case 2: Arterial acid-base and electrolyte studies. |</p>
<table>
<thead>
<tr>
<th>Time after induction (min)</th>
<th>Bicarb. adm. (m.equiv)</th>
<th>pH</th>
<th>Pco₂ (mm Hg)</th>
<th>BE (m.equiv/l)</th>
<th>K⁺ (m.equiv/l)</th>
<th>Na⁺ (m.equiv/l)</th>
<th>Cl⁻ (m.equiv/l)</th>
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<tr>
<td>60</td>
<td>-</td>
<td>6.96</td>
<td>52</td>
<td>-20</td>
<td>7.4</td>
<td>154</td>
<td>-</td>
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<tr>
<td>70-93</td>
<td>300</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>6.71</td>
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<td>93-155</td>
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<td>7.15</td>
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<td></td>
</tr>
<tr>
<td>155-265</td>
<td>-</td>
<td>7.27</td>
<td>57</td>
<td>-2</td>
<td>3.8</td>
<td>162</td>
<td>93.8</td>
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<tr>
<td>265</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>265-380</td>
<td>-</td>
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<tr>
<td>380</td>
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<td>852</td>
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</table>

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Sixteen minutes after arrest (93 minutes after induction) cardiac activity suddenly returned, with a normal c.c.g. pattern, a pulse rate of 160 beats/min, and a systolic blood pressure of 130 mm Hg. The rectal temperature was 41°C; cooling was continued. A urinary catheter was inserted, revealing absence of urine production at this or at any other time.

By 5 hours 27 minutes after induction, the temperature had begun to decrease significantly. When the rectal and oesophageal temperatures reached 35.7°C and 39.7°C respectively, all active cooling efforts were stopped. During this time the systolic blood pressure remained at 120–145 mm Hg, the pulse rate being 100–120 beats/min. Another 100 mg dose of hydrocortisone was administered.

After resuscitation (77–93 minutes after induction) the cardiovascular status was stable until about the time cooling was stopped (5 hours 27 minutes after induction). At that time generalized bleeding began to develop gradually. Over a period of two hours the previously dry operative site and all the cutaneous needle puncture sites began to bleed spontaneously. In addition, there were two copious loose bowel movements. Neurological evaluation revealed normal optic fundi and pupils which reacted sluggishly to light.

Seven hours 27 minutes after induction, the bleeding slowly continued to increase; calcium gluconate 1 g and cryoglobulin 14 ml were administered to facilitate clotting. There was no apparent effect. Surgical attempts to stop the bleeding from the operative site were also without effect. Fresh blood was ordered.

Seven hours 42 minutes after induction, there was still no sign of return of consciousness, even though the oesophageal temperature was 37.6°C and systolic blood pressure was 135 mm Hg. Knee jerks were absent and a right plantar reflex was present. Another 100 mg dose of hydrocortisone was given.

Seven hours 47 minutes after induction, intravenous mannitol and aminocaproic acid were added to the infusion. By 8 hours 52 minutes, however, mannitol 50 g had had no effect in instituting diuresis, and aminocaproic acid 14 g had also not affected the bleeding, which continued to increase slowly. The blood pressure was still normal, the pulse rate was 104 beats/min; spontaneous respiratory efforts were still apparent; a small amount of blood was aspirated from the trachea.

Phenoperidine 3 mg was given intravenously in divided doses to facilitate control of pulmonary ventilation by an East-Radcliffe ventilator. Manual ventilation was soon substituted because of decreasing compliance.

Eleven hours 17 minutes after induction, the blood pressure suddenly decreased to 60 mm Hg systolic. It responded well to the administration of intravenous Ringer-lactate solution.

Twelve hours 7 minutes after induction, fresh blood was available and was administered. The rectal temperature had gradually increased to 38°C since the cooling measures had been stopped.

By 13 hours 22 minutes after induction, two units of fresh blood had been administered. The blood loss, however, continued to increase slowly. Calcium chloride 1 g and calcium gluconate 1 g were again injected without effect. The systolic pressure gradually fell again to 60 mm Hg. The abdomen began to distend which was thought to be due to retroperitoneal or gastrointestinal bleeding. The pulmonary compliance decreased further, and excessively high inflation pressures were soon required to accomplish tidal volumes of even 100 ml.

The cardiovascular status continued to deteriorate rapidly in spite of a third unit of fresh blood. At 14 hours 12 minutes after induction, cardiac arrest occurred for the second time and was unresponsive to all resuscitative measures. Fourteen hours and 34 minutes after induction, the patient died.

Post-mortem examination revealed the effects of a bleeding diathesis. There were small amounts of blood in the peritoneal and pleural cavities. The hypophyseal stalk was haemorrhagic. Clots filled the smaller vessels in the oedematous brain. There were numerous punctate haemorrhages throughout the white matter. The lungs and bronchial tree were filled with blood leaving almost no aerated portions. The thyroid was somewhat enlarged (57 g). The liver had a crenated surface. There was surprisingly little atherosclerosis. The operative site extended into the left maxillary sinus. The only significant microscopic findings were invasive fibrous thyroiditis and fatty degeneration of the liver with biliary cirrhosis.

**COMMENTS**

Several reports (Leading Article, 1968; Editorial, 1966; Murray and Williams, 1969; Purkis et al., 1967; Relton, Creighton and Conn, 1968) have appeared documenting cases of malignant hyperpyrexia and propounding aetiological theories. We present here a number of questions and speculations which seem to reflect how unsatisfactory are the theories so far advanced.

First, is there any way of recognizing patients who are potentially "at risk"? There appears to be no common factor in any of the recorded pre-operative histories.

Are there any early signs of onset which, if recognized, might lead to earlier diagnosis and more successful treatment? There appears to be no constant mode of presentation, which fact is illustrated by our case reports. In case No. 1 hyperpyrexia preceded the increase in muscle tone, whereas in case No. 2 an increase in muscle tone occurred first, alerting us for a possible rise in temperature. To confuse the situation further, one of us (R.M.D.) recalls a patient who was anaesthetized eight times between April 1961 and November 1967. She received suxamethonium on seven occasions and on four of these exhibited exaggerated voluntary muscle tone, particularly of the jaw and neck muscles, once severe enough to make oral intubation impossible. On four occasions there was a delay of several hours in the return of adequate spontaneous ventilation. At no time was there any rise in body temperature. Might
this have been a modified form of the "malignant hyperpyrexia" syndrome?

Is this condition truly a new syndrome or is there any relationship between it and deaths from ether convulsions? Reports of fulminant hyperpyrexia have been published only during the last 8 years.

What is the trigger which sets off this metabolic explosion? This is perhaps the most important question. Further, what is the mechanism of the rise in temperature? Under resting conditions simple inability to lose heat will result in a temperature increase of 1.3°C per hour. Even in severe muscular exercise the rate of rise will not be as great as that exhibited by our second patient, i.e., 5°C in 20 minutes (Samson Wright, 1965). Thus, in these cases, there must be a greatly increased production of energy, which appears as heat.‡ But where and how does this energy production occur? Indeed, is it possible that the intense muscle activity is another result of the generalized physiological upset? To incriminate it as the source of energy production is unsatisfactory, for, as we have already said, hyperpyrexia may precede any increase in voluntary muscle tone. So, the question remains: what is the relationship between the hyperpyrexia and the increased voluntary muscle tone?

Is an inability to respond normally to increased body temperature a part of the syndrome? For example, our second case exhibited an intense peripheral vasoconstriction and an absence of sweating. May this reflect an interruption of the nervous pathways between the hypothalamus and the skin?

Is it significant that in most reported cases, including those recorded here, hyperpyrexia has developed about 45 minutes after induction of anaesthesia?

Is the disruption of the haemostatic mechanism yet another manifestation of the generalized disturbance, or is it purely secondary to the very high temperature? Our second case exhibited a severe bleeding diathesis of unknown aetiology. This has been reported in two cases (Purkis et al., 1967; Relton, Creighton and Conn, 1968). Clearly, there is a need for full haematological investigation, including clotting factors, in these patients as soon as the diagnosis of malignant hyperpyrexia is confirmed.

The ultimate question is: does cell death occur as a result of the process causing the pyrexia, or as a result of the very high temperature itself?

Until these questions are answered we will continue to be faced with the terrifying problem of a previously fit patient who develops this condition during anaesthesia, deteriorates rapidly, and dies. There is a more favourable mortality rate in children as compared to adults. This may be accounted for by the fact that their surface area is greater in relation to their body mass. They are, therefore, easier to cool rapidly.

At the present time, treatment of malignant hyperpyrexia occurring during general anaesthesia is symptomatic only. The fullest biochemical investigation should be instituted once diagnosis is established. This should include blood gas and serum electrolyte estimations at regular intervals. An extra aliquot of blood should be withdrawn each time so that retrospective studies may be performed.

One of the major problems in these cases is the lack of adequate monitoring facilities. The rectal temperature merely establishes that the pyrexial process is under way, by which time it may be too late. Tympanic membrane temperature monitoring may well prove to be a useful adjunct (Benzinger, 1963; Benzinger and Kitzinger, 1963).

Finally, we would suggest that perhaps a central committee of reference, under the aegis of the Association of Anaesthetists of Great Britain, should be set up. Details of new cases could then be reported to and analyzed by that committee, since there is a desperate need to collect more evidence of this ill-understood condition.

ACKNOWLEDGEMENTS

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REFERENCES


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**CAMBRIDGE UNIVERSITY MEDICAL SCHOOL**

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The fee for the complete course will be £30. Those attending for individual Saturday will only be liable for a fee of £2 2s. Enrolment forms and further details may be obtained from the Secretary, Cambridge University Medical School, Hills Road, Cambridge, CB2 1QT.

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**BRITISH JOURNAL OF ANAESTHESIA**

**HYPERPYREXIE MALIGNE: RAPPORT DE DEUX CAS**

**SOMMAIRE**

Un rapport détaillé de deux cas d'hyperpyrexie maligne chez deux hommes est présenté. Les deux patients sont décédés en dépit d'un diagnostic précoce du syndrome et d'un traitement vigoureux.

**MALIGNE HYPERPYREXIE: ZWEI FALLBERICHTE**

**ZUSAMMENFASSUNG**