Malignant hyperthermia in a black adolescent

Case report

T. P. LOMBARD, J. L. COUPER

Malignant hyperthermia (MH) is a rare genetic abnormality which presents in the peri-anesthetic period with tachycardia, hyperventilation, hyperthermia and acidosis. Untreated, the mortality rate is in excess of 80%. This syndrome is much less common in blacks than whites. A case of malignant hyperthermia in a black South African, in whom the reaction only became evident in the postoperative period, is reported. The case also presents several other unusual features.

Summary

Malignant hyperthermia is a rare genetic abnormality which presents in the peri-anesthetic period with tachycardia, hyperventilation, hyperthermia and acidosis. Untreated, the mortality rate is in excess of 80%. This syndrome is much less common in blacks than whites. A case of malignant hyperthermia in a black South African, in whom the reaction only became evident in the postoperative period, is reported. The case also presents several other unusual features.

At 11h20, after a short period of pre-oxygenation, the patient was induced with thiopentone 275 mg followed by suxamethonium 50 mg. After minimal fasciculations he was manually ventilated with a mask for 30 seconds and easily intubated with an 8.5 mm armoured endotracheal tube and the cuff was inflated. At no time was there any jaw stiffness. He was ventilated with a Manley Servovent ventilator via a Bain circuit. Fresh gas flow was 6 l/min (3 l nitrous oxide/3 l oxygen). Enflurane 3% was used to maintain anesthesia.

Shortly after the start of mechanical ventilation there was slight patient movement and, since the procedure was expected to be of short duration, suxamethonium 25 mg and thiopentone 50 mg was given. The heart rate decreased from 110/min to 45/min and atropine 0.5 mg was injected intravenously. The heart rate rose to 150/min. The blood pressure had been stable throughout this period at 120 mmHg systolic.

At 12h00 the patient was breathing well, his mucous membranes were pink and he was taken to the recovery room with the endotracheal tube in situ. He had not yet regained consciousness. By 13h00 the patient had extrabated himself but was still deeply unconscious. His arms were flexed and his fists were tightly closed. He had sinus tachycardia of 160/min and a respiratory rate of 40/min and was given oxygen by mask. The blood pressure was 140/90 mmHg. The anaesthetist who saw him at this stage thought this was an exaggerated pattern of recovery from anesthesia.

By 14h00, 2 hours 40 minutes after suxamethonium and 2 hours after termination of anesthesia, the patient had still not regained consciousness, had begun to sweat and had developed an opisthotonus posture with arms flexed. The authors were now informed of the patient's condition for the first time and on seeing him made the clinical diagnosis of malignant hyperthermia. The heart rate was 180/min, blood pressure 140/85 mmHg and respiratory rate 45/min. Rectal temperature, now taken for the first time, was 42.3°C.

Propranolol 1 mg intravenously, to decrease the heart rate, was immediately given and ice, cold intravenous fluids and dantrolene sodium were called for. He was hyperventilated manually with a mask and a high flow of 100% oxygen and covered with ice. Cold intravenous fluids were administered. At 14h15 the heart rate was 160/min, blood pressure 135/90 mmHg and temperature 42°C. Lyophilised dantrolene sodium (Dantrium; Eaton) 60 mg (3 x 20 mg vials) was administered over the next 10 minutes (i.e. 1.2 mg/kg). Diazepam 10 mg was also given intravenously in an attempt at sedation and to reduce muscle tone. At 14h25 the patient was intubated with difficulty because of increased masseter tone. No relaxant was used. He responded to this manoeuvre with increased flexion of arms and hands and extension of neck and back. When his posture returned to the pre-intubation state about 2 minutes later, the heart rate was 98/min, blood pressure 150/90 mmHg and temperature 40°C. An arterial line was inserted and a...
At 14h40 with the heart rate 97/min, blood pressure 120/90 mmHg and temperature 39.5°C, the patient was given procaine 200 mg intravenously and a further 20 mg dantrolene. Arterial and venous blood was sent for extended biochemistry, liver function tests and creatine kinase (CK) estimation (Table I). Significant values were: arterial serum sodium 129 mmoVl, K+ 5.4 mmoVl, total carbon dioxide 19 mmoVl and venous K+ 6.6 mmoVl.

The patient’s temperature continued to fall to 35.7°C but because of the ongoing rigidity a further 60 mg dantrolene (total dose now 140 mg; 2.8 mg/kg) was given and procaine 200 mg was repeated. His temperature fell rapidly to 35.5°C, heart rate 68/min and blood pressure (mean) 102 mmHg. All cooling was stopped but the temperature fell further to 34.5°C and the patient started shivering.

At 15h10 the patient was transferred to the intensive care unit where he was connected to a mechanical ventilator (tidal volume 10 ml/kg, rate 10 breaths/min, fractional inspiratory oxygen (Fio2) 1.0). The blood pressure (mean) was 120 mmHg, pulse rate 135, 0 134,0 19,4+ 18,91 mean blood pressure fell to 76 mmHg, while the heart rate remained at 70/min. He had received 500 ml balanced salt solution and morphine 10 mg intravenously since admission to the intensive care unit. His central venous pressure was 14 cm H2O. The peripheral cyanosis improved and the Fio2 was reduced to 0.4. The following treatment was started: dexamethasone 8 mg intravenously 8-hourly, ampicillin 500 mg intravenously 6-hourly, diazepam and morphine when necessary.

Four days after the anaesthetic a lumbar puncture and computed tomography (CT) were performed because of continued drowsiness, hyperreflexia, unresponsive pupils and episodes of unco-ordinated non-purposeful movements. Cerebrospinal fluid proteins were increased and CT demonstrated generalised cerebral oedema.

On the 6th postoperative day the patient was weaned from the ventilator and was successfully extubated the next day. He remained cerebrally depressed. Repeat CT was normal. By day 11 he had insight into his condition and was worried about his inability to walk. This improved over the following 2 weeks and he was discharged from hospital 37 days after the incident.

With regard to laboratory investigations: the patient’s CK continued to rise from 720 U/l (normal for laboratory 0-83 U/l) on day 1 to 2690 U/l on day 6 and had decreased to 82 U/l by day 19. CK iso-enzymes showed that the enzyme was coming predominantly from the muscle. Urine myoglobin was not assessed since the laboratory was not equipped to do so at the time, but renal function was good throughout the patient’s hospital course. While he was in hospital, a specimen of blood for assay of CK levels was
A CSC-H might have been because an initial dose of alY in which no increase rate of 4O/min recorded when the patient was first formed is kept cold, with the surgeon insisting on an ambient temperature of the theatre in which this operation was performed is kept cold, with the surgeon insisting on an ambient temperature between 12°C and 16°C. At least one report (MacGillivray et al.) implicates patient hypothermia induced for elective cardiopulmonary bypass soon after administration of triggering agents for delay in onset of the clinical signs of MH. It was noted by the anaesthetist during the early recovery of our patient that he was cold and this was thought to have contributed to the delay in onset of adequate spontaneous respiration. Unfortunately, no note was made of whether there was shivering in the postoperative period; whether shivering could have been a delayed triggering factor is therefore uncertain.

The patient did not awaken from anaesthesia in the 2 hours between the end of the anaesthetic and the diagnosis of MH. This delayed awakening might have been due to hypothermia from the cold theatre but is not a feature we see in other patients operated on in that particular theatre. There was no other apparent reason for the delay in awakening and we must speculate that the process of MH had already begun and somehow contributed to the patient not recovering normally. Perhaps the cerebral oedema which was documented on day 4 was already present and accounted for the patient remaining unconscious.

The diagnosis of MH was immediately considered 2 hours after the end of anaesthesia when we were called by the recovery room sister. The patient was then in opisthotonus and was very warm to touch. There was marked tachycardia and tachypnoea. Unfortunately, no clear history is available of events in the hour between when the patient was first seen in the recovery room and when the authors were called. The flexion of the arms, tight fists, tachycardia of 160/min and a respiratory rate of 40/min recorded when the patient was first seen in the recovery room should have suggested the diagnosis of MH. It is not certain whether the patient was pyrexial at that stage. Cases have been reported in which rigoridity did not occur immediately after suxamethonium administration but only began an hour or two later. There are a number of reported cases with all the other features of MH in which no rigoridity occurred at all.

The metabolic acidosis was mild for a reaction of this severity and at no time did the patient need bicarbonate therapy. The Paco2 was slightly low on the first specimen sent for blood gas analysis, but manual hyperventilation had already been started and 1 mg/kg dantrolene sodium already administrated. The pH was only slightly acidic at 7.322 although the BE was −7.1 mmol/l. Over the next 8 hours this returned to −1.0 mmol/l without any specific treatment. These relatively mild biochemical abnormalities, compared with those reported elsewhere, might have been because an initial dose of dantrolene 1 mg/kg had been given and hyperventilation instituted before arterial blood was first drawn for analysis. The protracted postoperative course (19 days) with delay of return of normal neurological function is also unusual but this may be explained by the delay in diagnosis of the condition as well as the severity of the attack in this patient. The dose of dantrolene administered initially (1.2 mg/kg), which was the dose recommended on a wall-chart protocol prepared by a pharmaceutical company a few years previously, was in retrospect obviously inadequate. The initial dose recommended now is 2.5 mg/kg as a bolus intravenous injection as soon as it can be prepared. If the condition continues to smoulder then an intravenous infusion of 1–2 mg/kg/3 h should be maintained until evidence of the reaction has disappeared. Procarbazine and β-blockers no longer have a place in the treatment of MH. It is important to realise that MH can occur in the postoperative period and, if this had been recognised by the anaesthetist who first saw the patient, the condition might have run a much less protracted course.

Correlation between the clinical findings, which were severe, and the equivocal muscle biopsy response (i.e. only significant
taken from each of his immediate relatives. Both mother and father had elevated levels, as did 1 brother and a sister (Table II). In an attempt to exclude diagnoses other than MH, blood was sent for measurement of thyroid hormone values. Stool, urine and blood specimens were also sent for porphyrin screening. These tests were all normal. Blood was sent for tetanus antibody titres 2 days postoperatively and repeated 2 weeks later. Antibody levels were normal and did not rise in titre.

A biopsy specimen was taken from the vastus lateralis muscle and the response to graded concentrations of caffeine from 2 mmol/l was noted. The caffeine-specific concentration was 16 mmol/l. At 1% halothane there was a 0.3 g increase in muscle tension. The muscle did not contract in response to enflurane. Enflurane in the presence of caffeine produced minimal increase in muscle tone. The caffeine-specific concentration in the presence of 1 vol % halothane (CSC-H) was 0.8 mmol/l. We can therefore classify the patient as type K according to Britz et al. A CSC-H of less than 1 mmol/l is probably diagnostic of MH. Plans are being made to do muscle biopsies on members of this family.

**Discussion**

There are a few interesting and unusual features in this case. Firstly, MH is unusual in blacks. We have reviewed over 230 cases in which the patient’s race was stated. Pelz and Carstens reported the first known case in a black patient in South Africa and from their hospital statistics the incidence could be as low as 1:250 000. In our hospital, which has been in existence since 1972, this is the only case that has been seen in 170 000 anaesthetics. Britz states that malignant hyperthermia has only been reported in Caucasians or patients of mixed race in South Africa. We are aware of 3 case reports in South African blacks. This is therefore the 4th case to be reported. The syndrome has also been reported in 6 patients of mixed race in South Africa, as well as in at least 3 white South African families.

Secondly, the signs of the acute attack (tachycardia, tachypnoea, muscle rigidity, sweating and pyrexia) occurred over 2 hours after the administration of suxamethonium. There had been no jaw rigidity with intubation or after the second dose of suxamethonium. Many authors report no rigidity after suxamethonium, although Britz states that malignant hyperthermia only has been reported in Caucasians or patients of mixed race in South Africa. We are aware of 3 case reports in South African blacks. This is therefore the 4th case to be reported. The syndrome has also been reported in 6 patients of mixed race in South Africa, as well as in at least 3 white South African families.

Britz holds that shivering, especially in cold weather, may induce MH but that the onset is slower than usual. The temperature of the theatre in which this operation was performed is kept cold, with the surgeon insisting on an ambient temperature between 12°C and 16°C. At least one report (MacGillivray et al.) implicates patient hypothermia induced for elective cardiopulmonary bypass soon after administration of triggering agents for delay in onset of the clinical signs of MH. It was noted by the anaesthetist during the early recovery of our patient that he was cold and this was thought to have contributed to the delay in onset of adequate spontaneous respiration. Unfortunately, no note was made of whether there was shivering in the postoperative period; whether shivering could have been a delayed triggering factor is therefore uncertain.

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**Table II. Creatine Phosphokinase Values in Immediate Family Members (Normal Laboratory Range 0 - 83 U/I)**

<table>
<thead>
<tr>
<th>Family Member</th>
<th>CK (U/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father</td>
<td>1251</td>
</tr>
<tr>
<td>Mother</td>
<td>1541</td>
</tr>
<tr>
<td>Sister 1</td>
<td>63</td>
</tr>
<tr>
<td>Sister 2</td>
<td>50</td>
</tr>
<tr>
<td>Sister 3</td>
<td>1251</td>
</tr>
<tr>
<td>Patient</td>
<td>82</td>
</tr>
<tr>
<td>Sister 4</td>
<td>51</td>
</tr>
<tr>
<td>Brother 1</td>
<td>77</td>
</tr>
<tr>
<td>Brother 2</td>
<td>841</td>
</tr>
</tbody>
</table>

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response to caffeine in the presence of halothane) is difficult to explain. Unfortunately the muscle was not exposed to suxamethonium. There appeared to be minimal reaction of the muscle biopsy specimen to enflurane (which was the inhalational agent our patient received) in the presence of caffeine compared with the response to halothane. This would place our patient in the K group according to Brit et al., i.e. a group of patients whose muscle contracts significantly only when exposed to caffeine in the presence of halothane and not to either agent alone. These authors state, though, that a positive contraction response to caffeine in the presence of caffeine is the most reliable test in the diagnosis of MH in individual cases.

Nelson et al. suggest that there is a range or spectrum of MH susceptibility in the population extending from phenotype N (normal) through phenotype K to phenotype H (MH-susceptible - MHS). The latter develop significant muscle contracture in vitro to halothane alone. Many relatives of people with a proven MH reaction have been identified as phenotype K and a percentage of phenotype K patients have developed complications suggestive of MH (masseter spasm, arrhythmia, tachycardia) after receiving suxamethonium. Rosenberg and Reeds believe that the K phenotype represents the whole gene pool of MHS people and that the halothane/caffeine-contracture test is too sensitive for use in the diagnosis of MHS. The European MHS group has established certain criteria for the diagnosis of MI and do not test specimens with caffeine in the presence of halothane - thereby eliminating the K group of Brit. Our patient would not have been labelled MHS by their criteria. Unfortunately, we did not test our patient's muscle in vitro with 2% halothane. If no contracture had developed at 2% our patient would have been classified as MHN (MH-negative). If the response to 2% halothane had been positive then the patient would have once again fallen into a 'grey' group called MH-equival (MHE). It is hoped that soon the laboratory diagnosis of MH will be standardised world-wide so that patients can be clearly classified as MHS or MHN for their own safety.

Another diagnostic marker used before the advent of the muscle contracture tests was the patient's resting CK value and the increase in CK after a suspected episode. Rosenberg and Reeds expects a 200-fold increase in CK after an episode of MH and also believe that muscle biopsy is not indicated in insistence on a 200-fold increase in CK value for diagnosis. It is hoped that soon the laboratory diagnosis of MH will be standardised world-wide so that patients can be clearly classified as MHS or MHN for their own safety.

In summary, a case of malignant hyperthermia in a South African black patient is reported with uncommon features: (i) no masseter (jaw) rigidity after suxamethonium administration; (ii) less severe biochemical abnormalities than expected; (iii) minimum response of the muscle biopsy specimen to caffeine or halothane alone despite a severe clinical reaction; and (iv) delay in the patient's recovery of normal neurological function.

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REFERENCES