

# The diagnostic dilemma of intraoperative hyperpyrexia in a malaria endemic area

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## Summary

Malignant hyperthermia (MH) is a serious and feared complication of general anaesthesia. The diagnosis of MH may pose a diagnostic dilemma, as its two most common signs tachycardia and hyperthermia are also common features of infections, transfusion and drug reactions. We report three cases of hyperthermia occurring during anaesthesia posing diagnostic dilemma in which two of the cases appear to be due to malaria. It is therefore suggested that all patients undergoing anaesthesia in a malaria endemic area should be investigated and treated for malaria if indicated preoperatively even when asymptomatic to prevent such diagnostic confusion.

**Keywords:** *Intraoperative fever, Malaria, Malignant hyperthermia.*

## Résumé

L'hyperthermie maligne (MH) est une complication sérieuse et redoutée dans le domaine d'anesthésie générale. Le diagnostic de (MH) pourrait poser un dilemme diagnostique. Ces deux signes qui sont les plus fréquents sont la tachycardie et l'hyperthermie, ils sont également les traits fréquents des infections de la transfusion et des effets de drogues.

Nous faisons un rapport de trois cas des hyperthermies qui se sont produit pendant l'anesthésie qui ont soulevé un dilemme diagnostique parmi lesquels deux de ces cas sont peut-être causé par le paludisme. Donc, nous proposons de faire en sorte que tous ces patients qui suivent un traitement anesthésie dans un milieu endémique du paludisme devront être examiné et soigné de paludisme s'il est indiqué d'une manière préopératoire même s'il est asymptotique afin d'éviter une telle confusion diagnostique.

## Introduction

Body temperature disturbance often accompanies anaesthesia with hypothermia being more common than hyperthermia<sup>1</sup>. The effects of general and regional anaesthesia on temperature balance are well established: thus routinely in the perioperative period defenses are mounted against hypothermia<sup>2</sup>. Hyperthermia occurring during surgery is always of grave concern because of the diagnostic dilemma and the possible unfolding pathology. The differential diagnoses of hyperthermia range from infections including malaria in the endemic regions, endocrine disorders such as thyrotoxicosis, blood transfusion and drug reactions to the rare but serious malignant hyperpyrexia (MH.) Detailed biochemical tests needed for cases of malignant hyperpyrexia (MH.), when not available could pose a major problem to diagnosis and method of management especially in a malaria endemic area as ours. We hereby report three cases illustrating such diagnostic and management problems that anaesthetists working in or visiting malarious endemic areas with minimal facilities must be aware of.

## Case 1

A 56-year old woman with carcinoma of the cervix presented for examination under anaesthesia and the fitting of applicators for caesium therapy. Her past medical history was unremarkable. She had been transfused with two units of blood six hours previously because packed cell volume was 22% from vaginal bleeding. At induction, she was afebrile, the pulse rate was 88 per minute, the blood pressure was 110/70 mm Hg and the respiratory rate was 16 cycles per minute. She was monitored by manual palpation of the pulse and the blood pressure with a mercury sphygmomanometer. Anaesthesia was induced with intravenous 50mcg fentanyl citrate and 250mg of thiopentone sodium and maintained with 60% nitrous oxide and 2 % of halothane in oxygen administered through a face mask using the closed circuit breathing system.

Within minutes thereafter, the respiratory rate increased to 32 per minute but the blood pressure remained normal while the pulse rate rose to 108 per minute. No malfunction was discovered on checking the breathing system and the breath sounds were normal. The patient was then noticed to be febrile; the temperature was 39°C. An intense generalised muscle rigidity and central cyanosis were also observed while attempting to insert an oropharyngeal airway in the mouth. A presumptive diagnosis of MH was made and the anaesthetic gases discontinued. One hundred per cent oxygen was administered and active surface cooling applied. Oximetry and arterial blood gases could not be monitored, as the facilities were unavailable. The surgical procedure was rapidly concluded within fifteen minutes with 50mg aliquots of thiopentone providing anaesthesia. The pulse rose to 144 beats per minute, respiratory rate to 50 per minute and the temperature to 42°C after termination of the volatile anaesthetic agents. Diuresis and cooling were encouraged with rapid infusion of 2 litres of cold saline. The serum potassium and bicarbonate were 5.1 and 23 mmol/L respectively but they had not been measured preoperatively. Dantrolene was unavailable for treatment and she was transferred to the ICU for further monitoring and symptomatic management with surface cooling and oxygen therapy by face mask. Two hours postoperatively the vital signs had improved: the temperature was 37.5°C, the pulse rate was 110 per minute the respiratory rate was 18 per minute and the blood pressure was 110/70 mm Hg. The patient was awake, alert and was later transferred to the Oncology ward. She was treated for malaria with oral chloroquine phosphate empirically. Detailed investigation for MH could not be carried out because the facility was unavailable in the hospital. Thus, she was informed of the complication and its implications for future surgery and a written medical alert was also issued to her.

## Case 2

A 15-year-old girl with recurrent tonsillitis presented for tonsillectomy. At preoperative visit history revealed no intercurrent illness and no anaesthetic experience. She had lost her father at the age of three years to some unknown illness, which was not related to anaesthesia and was being brought up by her

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grand parents as her mother had emigrated to the USA. She was afebrile and the cardio-respiratory system was normal with a heart rate of 86 beats per minute and blood pressure of 110/60mmHg. Premedication was declined.

At induction, the heart rate was 96 per minute, the blood pressure was 110/70mm Hg and the electrocardiogram (ECG) showed normal sinus rhythm. Anaesthesia was induced with intravenous thiopentone sodium 250mg and penthidine 25mg. A size 7.5mm cuffed Portex tracheal tube was placed after muscle relaxation with 100mg suxamethonium chloride. Anaesthesia was maintained with spontaneous inhalation of nitrous oxide 50% in oxygen and halothane 1.5-2.0%. During the dissection of the tonsil, the ECG showed ectopic beats and tachycardia of 140–150 beats per minute. A tachypnoea of 40 breaths per minute was also recorded which led to a suspicion of possible tube obstruction during dissection. Controlled manual ventilation was commenced with 6mg of pancuronium bromide providing muscle relaxation. The tachycardia however continued to rates of 180 per minute and muscle rigidity was then noticed. A 40°C body temperature was recorded from a rectal temperature probe. A diagnosis of MH was assumed, halothane was terminated and a fresh anaesthetic machine was used for the rapid conclusion of the right tonsillectomy with the left abandoned. Oximetric monitoring was commenced and oxygen saturation was 100%. The intravenous infusion was changed to cold normal saline and the rate was increased to about 1 litre per hour. A nasogastric tube was inserted for gastric lavage with cold saline, ice packs were placed around the major vessels in the axillae and the groin and surface cooling was applied. Blood was taken for full blood count, urea and electrolytes and creatine kinase estimation. She was ventilated with 100% of oxygen, the tachycardia worsened to 200 beats per minute with ensuing hypotension of 80/50mm Hg from the 100 – 110/60–70 previously maintained intraoperatively. The tachycardia was treated with lidocaine 100mg with a reduction in heart rate to 150 beats per minute after a second dose. Fifty millimol of bicarbonate was also administered empirically. The temperature peaked at 42°C within 20 minutes of the commencement of recording before observation of a slow response to treatment. After lidocaine administration, temperature fall was precipitous with ensuing hypothermia of 35°C. The treatment was also complicated by pulmonary oedema, which responded to furosemide. She was transferred to the Intensive Care Unit where she was to be ventilated and warmed overnight. She was deeply comatose but haemodynamically stable. The results of the electrolytes were normal but the creatine kinase could not be done for logistic problems. She regained consciousness in the night about 12 hours after the procedure and self-extubated. She subsequently made a rapid recovery. She could not be fully screened for MH because there was no facility for the test in Nigeria but the complication was explained to the grandparents and the patient both verbally and in a medical alert document.

### Case 3

A 7-month-old male child was scheduled for elective repair of left cleft palate. The child had an uneventful general anaesthetic of nitrous oxide and halothane in oxygen for the repair of left cleft lip at the age of three months. There was no history of blood transfusion or drug allergy.

The patient is a product of full term pregnancy and the antenatal period and delivery were uneventful. Preoperative clinical condition was satisfactory. He was afebrile, with a pulse of 134 beats per minute, normal heart sounds and clinically clear lung field. The packed cell volume (PCV) was 30% and the

haemoglobin genotype was AA. Sedative premedication was withheld. The temperature on the morning of the operation was 36.8°C. He weighed 10kg.

The pre-induction vital signs were respiratory rate of 30 cycles/minutes, heart rate of 140 beats per minute and oxygen saturation of 100%. Anaesthesia was induced with nitrous oxide in oxygen at 3L/minute each and halothane 0.8–3.0 vol.% via the infant circuit. One (1)mg of pancuronium bromide was administered intravenously to facilitate oro-tracheal intubation with a size 4.0mm Portex tube. The oro-pharynx was packed with wet gauze. Anaesthesia was thereafter maintained with 50% nitrous oxide in oxygen and 0.5–0.8% halothane. Intravenous pentazocine 5mg was administered for analgesia.

The heart rate post induction was 140 beats per minute until the gag was inserted and it increased to 160 per minute. With the commencement of surgery, this further went up to 170–180 per minute. Ascribing this to light anaesthesia, halothane was increased to 1% but without appreciable effect for the duration of the procedure. The heart rate rose on some occasions to 200 beats per minute. At the conclusion of the procedure, which lasted about one hour, the patient was noticed to be febrile to touch and axillary temperature was 38.2 Celsius. There was however no muscle rigidity. Malignant hyperthermia was suspected and halothane was discontinued and the patient was maintained on 100% oxygen with a new breathing system. Active surface cooling was applied and 500mg dipyron was administered intravenously. With the reduction of the heart rate and the temperature to 140–160 beats per minute and 37.5 Celsius respectively, the residual effects of muscle relaxants were reversed and the child was transferred to the recovery room. An examination of the blood film for malarial parasites was ordered but creatine kinase estimation to aid in the diagnosis of MH could not be performed due to logistic reasons. The blood film showed parasitaemia and the child was treated for malaria with oral chloroquine to which the fever responded. The parents were informed of the complication and a medical alert issued.

### Discussion

The major diagnostic apprehension in these three cases was the possibility of MH, an inherited disorder of skeletal muscle which presents with muscle hypermetabolism when triggering anaesthetic agents are used. MH is more common in children and young adults, rare in infants and the incidence declines after the age of 50 years. The mortality associated with the disease is 80% before treatment with dantrolene was discovered and has been reduced to 10% with dantrolene use<sup>3</sup>. Early diagnosis and treatment are therefore of paramount importance and may lead to misdiagnosis of other causes of intraoperative hyperthermia for MH.

The most common triggering agents for MH are the volatile anaesthetic agents such as halothane and suxamethonium which were used in these cases. The signs of MH are non-specific; they could be observed in the preoperative patient as a concurrent disease, during an inadequate anaesthesia or faulty anaesthetic technique, or equipment malfunction. The signs include tachycardia, tachypnoea, hypercarbia, respiratory and metabolic acidosis, muscle rigidity, rapid temperature rise; arrhythmias, hyperkalaemia and myoglobinuria. In defining a clinical grading scale to predict malignant hyperthermia Larach *et al*<sup>4</sup> developed six indicators for MH and these included a positive family history, muscle rigidity, respiratory acidosis, temperature increase, cardiac involvement and biochemical evidence of muscle breakdown. None of the three cases presented

had a positive family history but were presumed to have MH based on inappropriate tachypnoea, rapid increase in temperature in preoperatively afebrile patients and inappropriate tachycardia exhibited after exposure to triggering anaesthetic agents. While the muscle rigidity observed in the second case is more indicative of MH, that in the first case posed diagnostic dilemma in view of the recent blood transfusion. Apart from transfusion reactions that may be apparent during the blood administration, in malaria endemic areas, malaria parasites may be acquired through a transfusion (donors are not screened for malaria) resulting in clinical manifestations such as fever, tachycardia and rigors under anaesthesia<sup>5,6</sup>. Furthermore, a study by Ajao<sup>7</sup> identified malaria as the most common cause of postoperative fever in Nigeria, a malaria endemic area, suggesting that the patients must have been asymptomatic preoperatively. In case 3 the possibility of malaria was also entertained because his previous anaesthetic experience as documented was uneventful and MH is not common in the infant<sup>8</sup>. At that age however the child may be having the first malaria attack at a time when the maternally acquired immunity to malaria is exhausted and the child's defenses are not yet fully developed<sup>9</sup>. Conversely the presence of malaria parasites in the blood film does not conclusively ascribe the intraoperative fever to malaria since healthy children have been observed with parasitaemia<sup>10</sup>. This notwithstanding, perhaps it is prudent to adopt the earlier suggestion of Ajao<sup>7</sup> and routinely administer antimalarial agents to patients when they are scheduled for surgery as the immunosuppressive effects of anaesthesia and surgery may convert an incubating or quiescent parasitaemia to an active infection both intra and postoperatively.

The diagnosis of the hyperthermia could have been aided in these cases with the non invasive capnography to monitor end tidal carbon dioxide or arterial blood gas monitoring for carbon dioxide tension. After other causes of intraoperative carbon dioxide retention have been excluded, inappropriate hypercarbia resulting from the hypermetabolism is the most sensitive clinical feature of MH and has not been described as a feature of malaria or other infections.

With the paucity of both monitoring and diagnostic facilities, an incontrovertible cause of the hyperthermia in these three cases could not be claimed hence the institution of the MH management regime. Our management limited to symptomatic treatment such as stoppage of the triggering agents and 100% oxygen administration, active cooling of the patient, correction of acidosis and hyperkalaemia and encouragement of diuresis should ideally include dantrolene administration<sup>11</sup>. Dantrolene is the agent of choice both for MH prophylaxis and definitive treatment. It is a hydantoin derivative, which decreases the release of calcium from the sarcoplasmic reticulum and reverses an MH episode. The initial dose is 2-3mg/kg intravenously as soon as MH is suspected and up to 10mg/kg can be administered to eliminate all the signs of MH. Dantrolene 1mg/kg every 6 hours for 24 to 48 hours is also recommended after the acute phase to prevent recrudescence of the signs<sup>11</sup>. Dantrolene was not available in our center because the drug is expensive and being rarely requested for, was not stocked by the pharmaceutical suppliers. The response of the second patient to lidocaine was not surprising since in the pre dantrolene era procainamide was employed in the treatment of MH but with inconsistent results<sup>12</sup>. Current management however employs the antiarrhythmic effect of lidocaine in the treatment of the acidosis and hyperkalaemia induced dysrhythmias of MH<sup>13</sup>. The definitive diagnosis of MH susceptibility remains the caffeine, halothane and ryanodine in vitro muscle contracture tests<sup>14</sup>. The tests

involve the biopsy of fresh muscle under local anaesthesia and the exposure of the specimen to caffeine or halothane environment. Larger contractures are observed in the muscles of MH susceptible compared to normal individuals. When these confirmatory tests cannot be performed due to non-availability of the facility as in our institution or for other reasons, it is mandatory that a detailed oral explanation about the complication and a written medical alert document should be issued to the patient to avert a future anaesthetic catastrophe.

In conclusion this report highlights the possibility of malaria as a cause of intra-operative hyperthermia. In malaria endemic areas. We suggest screening and treating for malaria as part of the preoperative investigation, and during intra-and post-operative hyperthermia.

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