Malignant hyperthermia: a possible new variant

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A young healthy male, who had three consecutive episodes of postoperative hyperthermia was anaesthetized with special precautions to prevent malignant hyperthermia. Despite neuroleptic anaesthesia and dantrolene pretreatment, the patient experienced post-anaesthetic hyperthemia. The patient's clinical picture was almost identical to the symptoms experienced by two of his maternal relatives. All three experienced nausea, vomiting, muscle cramps and high fever which occurred between five to seven hours after general anaesthesia. The serum potassium (K) and creatinine phosphokinase (CPK) levels determined during the hyperthermic episode and on the next day were not elevated. On the basis of the patient's family history, his clinical picture, and his laboratory data, we speculate that this patient might have a form of malignant hyperthermia or a possible new variant.

Key words
HYPERTHERMIA: malignant, postoperative; GENETIC FACTORS: hyperthermia.

The syndrome of malignant hyperthermia (MHS) has been well documented and publicized. However, there are still many unanswered questions about the syndrome.[1-4] One of the unanswered questions is the occurrence of hyperthermia in the postoperative period. Another is the failure of dantrolene pretreatment and neuroleptic anaesthesia to prevent the MHS.

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Since the acceptance of dantrolene and neuroleptic anaesthesia as the method of choice in giving general anaesthesia to the MHS-susceptible patients, several cases have been reported describing either failure of the "safe" anaesthestic method or an occurrence of postanaesthetic hyperthermia.[5-9]

We had the occasion to give anaesthesia to a patient who had experienced three previous episodes of marked hyperthermia, nausea and vomiting. All three attacks occurred between five to seven hours postoperatively.

Despite dantrolene pretreatment and administration of neuroleptic anaesthesia, the patient had another episode of postoperative hyperthermia, similar to the other three.

The description of the patient's clinical history and laboratory findings along with his family's medical history, might assist in understanding the nature of MHS.

Case report

The patient came for an anaesthesia consultation two weeks prior to his elective surgery, due to the three previous episodes of postanaesthetic fever, nausea, vomiting and the unusual medical history of his family.

Three months previously, while on a family vacation in a resort area, the patient sustained a fracture of his left forearm and underwent general anaesthesia for emergency surgery. Several hours after the surgery he suffered nausea, vomiting and muscle cramps. His oral temperature rose to 38.4°C and remained elevated for several hours. The anaesthetic drugs used were unknown to the family.

After returning home from vacation, 18 days after the injury occurred, he underwent general anaesthesia again for closed reduction, on an outpatient basis. Anaesthetic drugs used were: thiopentone, nitrous oxide, enflurane, and succinylcholine. Six hours after anaesthesia, at his home, he again suffered muscle cramps and his oral tempera-

ture rose to 40.4° C. Both conditions lasted several hours.

Three weeks after the injury, a third general anaesthetic was given for open reduction and internal fixation, on an inpatient basis. The anaesthetic agents used were: thiopentone, nitrous oxide, halothane, and succinylcholine. A few hours later, nausea, vomiting, and muscle cramps developed again and his oral temperature reached 41.0° C.

As a child, the patient had undergone general anaesthesia for tonsillectomy and adenoidectomy, without any apparent problems. The patient denied having cardiopulmonary, metabolic, renal, musculoskeletal, or hepatic disorders.

Review of the patient's family history suggests his symptoms are hereditary (Figure 1). One of his maternal aunts experienced symptoms similar to the patient's after her last two surgical procedures which she underwent as an adult. Like the patient, she had no symptoms after tonsillectomy performed during her childhood.

The patient's maternal grandfather, who was a medical doctor, suffered similar episodes on three occasions during his later years. He died of gastric cancer at the age of 70. No member of the family has any physical or mental deficits.

Upon physical examination, the patient was found to be a 16-year-old male of normal growth and development, intellectually bright and physically fit except for a complete low-median and ulnar nerve paralysis. His weight was 60 kg, blood pressure 120/70 mmHg, and pulse 80/min. No abnormal physical findings were noted. Preoperative laboratory data, which were collected twice, a week apart, showed CPK total 105/151 u/l (normal 8–132 u/l); CPK mB 14/16 u/l (normal 10–25 u/l), serum potassium (K) 5.4/5.6 mml/l (normal 3.5–5.0 mmol/l); and alkaline phosphate 210 u/l. CBC, urinalysis, chest *x*-rays, and EKG findings were within normal ranges.

The patient was admitted to our hospital, two days prior to the elective procedure for decompression of ulnar and median nerves. As a preoperative treatment he received 400 mg dantrolene orally (100 mg two times, then 50 mg four times, every six hours). The anaesthetic gas machine was purged overnight with 100 per cent oxygen. The anaesthetic tubing and soda lime were replaced with new units. One hour prior to the induction of anaesthesia, the patient received 100 mg of secobarbitone orally.

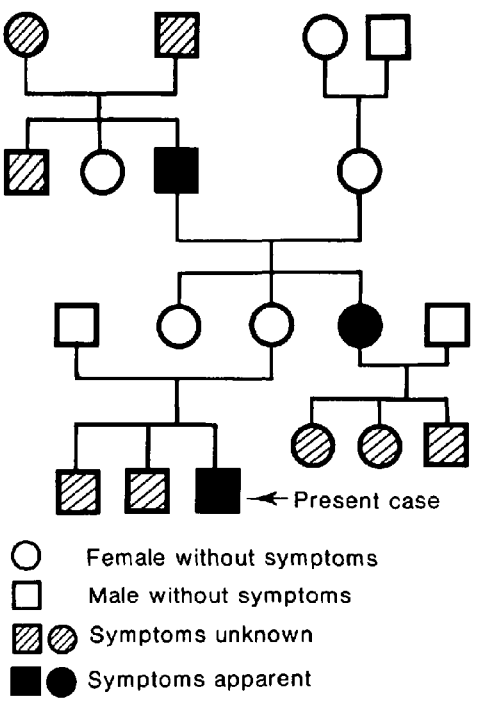

FIGURE 1 Family tree of the present case. Dark symbols indicate subjects who had typical symptoms. Striped symbols represent those who may or may not have symptoms. (Lack of information or the subjects have not reached adolescence yet.) The unmarked symbols indicate subjects who had no symptoms after anaesthesia.

Under appropriate monitoring and precautions for MHS, he underwent general anaesthesia. He received 325 mg thiopentone; 0.35 mg fentanyl; 5.0 mg droperidol; 8 mg pancuronium; and 60 per cent nitrous oxide, and had an uneventful anaesthetic course which lasted two hours. All vital signs, arterial blood gases, and laboratory findings were normal. Oral temperature ranged from 36.2° C to 36.5° C. After a two-hour stay in the recovery room the patient was transferred to the Intensive Care Unit (ICU) for further observation. Five hours after anaesthesia, the patient, still drowsy, became flushed. During the next 30-minute period, his skin became dusky and cyanotic and his temperature started to rise slowly. The cyanosis appeared on the periphery of the body and later spread over the chest and face. The patient also had a mild tremor of the

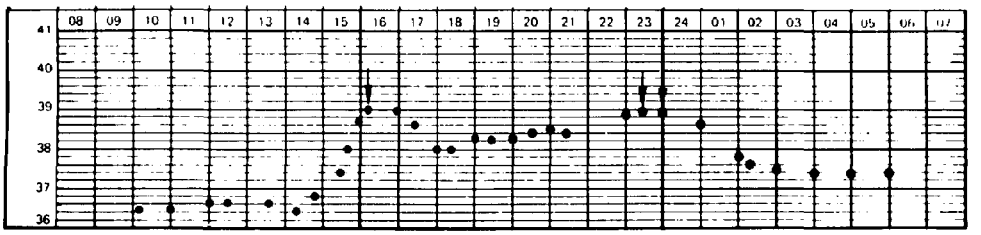

FIGURE 2 Temperature scale in centigrade on the Y-axis. Actual time of day appears on top of the figure on the X-axis. Each dot represents temperature of the patient, taken with a rectal temperature probe. Each of the three arrows represents 60 mg of dantrolene given intravenously.

shoulders. At that point, treatment for MHS was started. The patient was treated with 60 per cent oxygen by mask, gastric lavage with ice-cold saline, surface cooling, 50 mEq sodium bicarbonate and 60 mg dantrolene IV.

Despite this treatment, the patient's temperature rose to 39° C, pulse rose from 80 to 100 and then to 120/min. Respiratory rate went from 16 to 32/min. Blood pressure rose from 110/70 to 160/100 mmHg. A total of 180 mg dantrolene was given intravenously (Figure 2). The arterial blood gas drawn while the patient was receiving 60 per cent oxygen showed pH 7.29, PCO_2 44 mmHg, PO_2 158 mmHg and BE − 5. The patient remained in the ICU for twenty-four hours and received an additional 150 mg dantrolene orally (50 mg three times every six hours). The pertinent laboratory data obtained during hyperthermia and the next day were as follows: K 4.1/4.7 mmol/l; Ca 8.7/8.8 mg/dl; CPK total 69/68 u/l; CPK mB 11/17 u/l; platelets 256000/295000; and serum fibrinogen 187 mg/dl. Serum myoglobin was negative.

The patient was discharged from the hospital on his third postoperative day, without any residual effects.

Discussion

Despite neuroleptic anaesthesia and dantrolene pretreatment to prevent MHS, the patient experienced the same episode of postanaesthetic hyperthermia that had occurred previously when potent inhalation anaesthetic agents and a depolarizing muscle relaxant were used.

The anaesthetic method applied to the present case is known to be a 'safe' method and has been used successfully in over 500 MHS-susceptible patients.[1-3] 'Light anaesthesia' might have been suspected as the triggering cause, but the patient was adequately anaesthetized and had remained sleepy in the recovery room. The nurse who took the patient to the ICU, two hours after anaesthesia noted: 'patient very drowsy.' If the anxiety or physical stress had been the triggering factor of his symptoms, the patient could have experienced such an episode without undergoing anaesthesia.[1-4] Moreover, the patient is very active in sports and is under no medical restrictions.

The amount of dantrolene given preoperatively might be disputed.[10] However, MHS-susceptible patients have been successfuly anaesthetized with oral dantrolene pretreatment ranging from 2.2 to 10 $mg \cdot kg^{-1}$.[1,3,5,6] Gronert also reported a case in which a patient developed MHS while awake and was treated orally with a total of 1.1 to 2.2 $mg \cdot kg^{-1}$ dantrolene.[11]

In addition to those debatable points, the present case showed three other interesting facts. First, the symptoms were not apparent during childhood but appeared after adolescence. Three persons from two generations on the patient's maternal side were medical doctors but knew of no physical or mental deficits in the family.

Second, according to the patient's mother the symptoms were almost identical in each case. The mother knew all three relatives who had similar postoperative symptoms. Most MHS patients are known to have variable symptoms and signs. However, the moment the mother saw her son, almost one hour before his temperature started to elevate, she knew that he was getting an attack.

Third, although the patient experienced the same symptoms and temperature elevation (up to 39° C)

as he did without the MHS precautions being taken, the laboratory data obtained during and twenty-four hours after the attack did not correlate with the data of typical MHS.[1,3,5] Serum and urine myoglobin were negative and liver function tests were normal. However, serum Ca and K, CPK total, and CPK mB were much lower than the values obtained preoperatively.

We were unable to find any other published case in which the clinical picture and family medical history are comparable to the case presented. Without doing a muscle biopsy, we can only speculate that the present case may be another variant of MHS, or a different form of postanaesthetic hyperpyrexia.

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Résumé

Un jeune homme en bonne santé ayant présenté trois épisodes consécutifs d'hyperthermie post-opératoire a été anesthésié avec des précautions spéciales afin de prévenir l'hyperthermie maligne. Malgré l'anesthésie au neuroleptique et l'administration préalable de dantrolène, le patient a démontré des signes d'hyperthermie post-anesthésique. Le tableau clinique du patient a été presqu'identique aux symptômes présentés par deux membres de sa parenté maternelle. Tous les trois ont eu des nausées, vomissements, crampes musculaires et température élevée survenant entre cinq et sept heures après l'anesthésie générale. Le potassium sérique (K) et la créatinine phosphokinase (CPK) mesurés lors de l'épisode hyperthermique et le jour suivant n'étaient pas élevés. Sur la base de l'histoire familiale du patient, son tableau clinique et ses données de laboratoire, on présume que ce patient peut avoir une autre forme d'hyperthermie maligne ou possiblement une nouvelle variante.