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Recrudescence after Survival of an Initial Episode of Malignant Hyperthermia

ALIX MATHIEU, M.D.,* ARMEN J. BOGOSIAN, M.D.,† JOHN F. RYAN, M.D.,‡
ROBERT K. CRONE, M.D.,§ DEAN CROCKER, M.D.¶

Malignant hyperthermia is a fulminant hypermetabolic response of patients to anesthetic drugs, related to an elevated myoplasmic calcium level.[1,2] The steps in treatment of the initial acute episode have been adequately described.[3] We report two cases in which the patients survived the initial severe episode only to succumb to a recrudescence of the process many hours later.

REPORT OF TWO CASES

Patient 1. A muscular, 20-year-old, 104-kg, 190-cm man had a closed, comminuted fracture of the left tibia and fibula. There was no significant past medical history, and the results of physical examination were unremarkable. The family anesthetic history was negative. Anesthesia was induced with thiopental 300 mg, iv, with use of succinylcholine, 160 mg, iv, to facilitate endotracheal intubation. Endoscopy was performed with some difficulty due to insufficient relaxation. Anesthesia was maintained with nitrous oxide, 3 l/min, oxygen, 2 l/min, and halothane 2 per cent. Relaxation was obtained with pancuronium, 6 mg, iv. Within 10 min, the hyperpyrexia syndrome started, with an increase in esophageal temperature to 42 C, hypotension, and cutaneous signs of hypoxia. At their worst values, arterial blood-gas values ($F_{I_{O_2}}$ 1.0) were *p*H 6.96, P_{CO_2} 73 torr, and P_{O_2} 320 torr. The patient was immediately given gastric lavage with cold saline solution and packed in ice. Treatment also included bolus intravenous injections of sodium bicarbonate, 200 mEq, procainamide, 300 mg, and lidocaine, 100 mg, for ectopic ventricular beats, and continuous infusion of dopamine, 10–20 μg/kg/min. Furosemide, 100 mg, and mannitol, 5 g, iv, were also administered. These drugs were administered intermittently until blood gases were restored to normal values.

After active treatment for the initial episode of malignant hyperthermia, the patient was successfully treated for diffuse intravascular coagulation. Twelve hours after the initial episode, the patient was awake and asking for food. At this point, cardiovascular dynamics were stable, respiratory function was good, and the patient was no longer acidotic. His condition remained stable for the first 20 hours except for continued slight muscle rigidity, increased fluid volume requirement to maintain an adequate central venous pressure (CVP), and inadequate urinary output. Leg abduction and arm flexion produced moderate resistance throughout the postoperative period. Thirty hours after the initial episode, the patient suddenly became apprehensive, had masseter spasm, and became cyanotic, dyspneic and tachypneic. Despite hyperventilation with oxygen, within 20 min he had a cardiac arrest. The presumptive diagnosis of cardiac arrest due to hyperkalemia and recrudescence of malignant hyperthermia was made, and cardiopulmonary bypass and renal dialysis were rapidly instituted. The patient's temperature at this point was 36 C, and he remained afebrile until death. The first serum potassium value obtained after establishment of bypass was 14.2 mEq/l. Arterial blood-gas values were *p*H 6.94, P_{O_2} 400 torr, and P_{CO_2} 54 torr. A regimen of procainamide, 15 mg/kg, dantrolene 1.5 g, iv, mannitol, glucose, sodium bicarbonate, insulin, and cooling was instituted. When the serum potassium fell below 7.8 Eq/l the heart spontaneously defibrillated. Despite vigorous dialysis, potassium could not be reduced to below 6.6 mEq/l. With vasopressor support, an unsuccessful attempt was made to wean the patient from bypass. He succumbed to pulmonary edema and heart failure. Muscle biopsy while the patient was on cardiopulmonary bypass demonstrated a markedly diminished calcium intake into the sarcoplasmic reticulum, a characteristic finding of the syndrome.

Patient 2. A 31-year-old, extremely muscular, 102-kg, 177-cm man was admitted for bilateral inguinal herniorrhaphies. He had no prior history of surgery, and except for an allergy to tetracyclines, had no significant medical or family history, including abnormal responses to anesthesia. This patient was anesthetized in the same way as Patient 1, using thiopental, succinylcholine, halothane, and pancuronium.

The initial episode was characterized by cyanosis, a pulse-rate increase to 160 beats/min, a rapid rise in temperature to 41 C, and central venous blood-gas values of *p*H 6.72, P_{O_2} 29 torr, and P_{CO_2} 250 torr. Cooling was initiated with intravenous infusion of iced lactated Ringer's solution, approximately 4 l in one hour, in addition to gastric and bladder lavage with cold saline solution. Treatment also included bolus intravenous injections of procainamide, 200 mg, sodium bicarbonate, 450 mg, chlorpromazine, 25 mg, insulin, 20 U, and hydrocortisone, 300 mg. Cardiopulmonary bypass was instituted in this case also, and the patient survived the initial episode. He slowly awoke and became fully conscious 16 hours after the initial episode, and the trachea was extubated. Hours later, in the recovery room, he experienced increasing rigidity of all extremities. The temperature rose to 37.8 C eight hours after recovery, but decreased to 37.2 C 12 hours later, and the patient was afebrile at the time of cardiac arrest. Despite increased fluid administration, CVP remained low, urinary output decreased, and weight increased 24 kg in 30 hours. Serum potassium rose from 4.4 to 8.3 mEq/l, in spite of Kayexalate® enemas, peritoneal dialysis, mannitol infusion, and glucose and insulin therapy. Cardiac arrest occurred

* Assistant Professor of Anaesthesia, Harvard Medical School at the Massachusetts General Hospital.

† Clinical Fellow in Anaesthesia, Harvard Medical School at the Massachusetts General Hospital.

‡ Associate Professor of Anaesthesia, Harvard Medical School at the Massachusetts General Hospital.

§ Instructor in Pediatrics (Anaesthesia), Harvard Medical School at the Massachusetts General Hospital.

¶ Assistant Clinical Professor of Anaesthesia, Harvard Medical School at the Children's Hospital Medical Center.

Received from the laboratories of the Department of Anaesthesia, Harvard Medical School at the Massachusetts General Hospital, and the Children's Hospital Medical Center, Boston, Massachusetts 02114. Accepted for publication March 11, 1979.

Address reprint requests to Dr. Mathieu at his new address: Professor of Anesthesiology, University of Texas Medical School, 6431 Fanin, Room 5020, Houston, Texas 77030.

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when serum potassium was 8.8 mEq/l. The patient was resuscitated, but despite pressor infusion, initiation of hemodialysis was not tolerated, and he died.

Discussion

The recrudescences of malignant hyperthermia in the cases described above have several distinct features: 1) anxiety; 2) continued and progressive muscle rigidity; 3) hyperkalemia; 4) oliguria or anuria; 5) sequestration of fluid in muscle with increased fluid requirements.

Anxiety has been implicated by many investigators as a causal factor in initiation of the syndrome.[4–6] The first patient's apprehension appeared to lead directly to the recrudescence of malignant hyperthermia. The second patient's wife revealed that her husband had become "stiff" when excited or nervous, and even coffee "caused his muscles to tense." The patient reportedly had been terrified of surgery and especially worried that some complication might occur. The relation of anxiety to the onset of the syndrome recently has been documented in pigs and in man by Wingard *et al.*[4] who demonstrated that the acute syndrome can be triggered by emotional upset. For the same reason, Britt *et al.*[7] have also advocated the use of heavy premedication prior to subsequent anesthetic administration to individuals who have survived an initial episode of malignant hyperthermia.

Continued and progressive rigidity was prominent in both cases. The relationship of sustained contracture to a low-grade smoldering of the syndrome is not clear, but sustained contracture should be regarded as an ominous sign. It is important to determine the presence or absence of rigidity after initial successful therapy for malignant hyperthermia. Treatment must be maintained until the clinical evidence of muscle contraction has subsided. In view of the continuous rigidity in both patients, and in particular, of masseter spasm in the first patient, determination of serum calcium, which were not done, could have been of interest to rule out tetany as a causal factor.

The rise in serum potassium follows a change in muscle membrane permeability secondary to elevated myoplasmic calcium concentrations.[8] In Patient 1, despite hemodialysis, membrane permeability was altered so radically that when hemodialysis was temporarily halted, serum potassium rose from 6.6 to 8.9 mEq/l in 15 min. Hemodialysis should be instituted if potassium concentrations rise after the syndrome has apparently subsided. This therapy should not be withheld to await the classic signs of renal failure.

In spite of dopamine infusion and administration of sodium bicarbonate, mannitol and furosemide, the first patient's condition deteriorated. Renal failure ensued, with blood urea nitrogen (BUN) 44 mg/dl and creatinine 4.9 mg/dl. Postmortem examination demonstrated focal necrosis and pigmented casts, in addition to tubular degeneration. In Patient 2, however, oliguria occurred despite administration of diuretics and massive fluid infusion postoperatively.

The steps in treatment of the initial acute episode and late complications have been described.[9,10] This report describes the cases of two patients who recovered from the initial episode of malignant hyperthermia but later experienced mild to moderate muscle rigidity, oliguria or anuria, hyperkalemia, and death. Both patients lost muscle membrane integrity, with marked weight gains from translocation of fluid. It is fair to point out that in both cases, it is difficult to ascertain unequivocally whether the syndrome was smoldering during the apparent quiescent periods or whether the patients had fully recovered.

Recognition of these only partially attenuated lesions of malignant hyperthermia should be followed by vigorous monitoring of arterial blood gases, and renal, muscular, and neurologic function, and reinstitution of support and drug therapy with procainamide (15 mg/kg, iv) and dantrolene (10 mg/kg, iv) until symptoms subside.

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