

Dental treatment of a malignant hyperthermia-susceptible child

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Abstract

Malignant hyperthermia is a genetically transmitted complication of general or local anesthesia, with a high mortality rate. The literature is reviewed in relation to the etiology, diagnosis, clinical features, and treatment of a crisis. A case is presented which demonstrates the management of a malignant hyperthermia-susceptible child requiring dental restorations.

Episodes of malignant hyperthermia (MH), precipitated by anesthetic agents, are rare but often fatal if untreated. Early diagnosis of MH-susceptible (MHS) patients has lowered the mortality rate from 80% to 50-60%.¹ Dental practitioners and personnel should be aware of this life-threatening syndrome since both general and local anesthetics may trigger an incident. The purpose of this paper is to familiarize the reader with the disease entity; its manifestations, treatment, and prevention, and to examine a case involving treatment of an MHS child.

Frequency and Etiology

MH may occur at any age, although young patients have a higher prevalence. Forty per cent of the reported cases of precipitated MH are in patients younger than 14 years of age² and approximately 1 in 14,000 anesthetics in children and 1 in 50,000 anesthetics in adults. Males are affected more than females.³

The syndrome may develop after a single anesthetic exposure or after several asymptomatic anesthetics. Any potent inhalation agent or neuroleptic agent can trigger MH. Skeletal muscle relaxants, such as succinylcholine chloride, are the most prominent of all triggering agents, causing the most rapid onset of rigidity. Local anesthetics of the amide group also have been implicated in inducing MH.^{4,5} Safe general

anesthetics include nitrous oxide, barbiturates, pancuronium bromide and opiates.

Both a genetic predisposition and a triggering agent are required to induce MH; Henschel and Locker found 130 affected individuals, most of whom were of Scandinavian origin.⁶ MH now appears to be the result of multifactorial inheritance with gradations of susceptibility.^{4,5,7} MH induced by stress, trauma, and exercise has been reported in swine,⁵ but these etiologies have not been proven to precipitate the syndrome in humans.

Definitions and Diagnosis

Two syndromes of MH have been described; a rigid and a nonrigid form. The basic metabolic defect in the rigid form lies in the muscle metabolism of calcium. On a cellular level, there is a triggered release of Ca⁺⁺ from the sarcoplasmic reticulum into the intracellular cytoplasm.⁸ The increased Ca⁺⁺ concentration in the cytoplasm produces sustained contracture of skeletal muscle and a hypermetabolic state. The high cytoplasmic Ca⁺⁺ activates phosphorylase kinase, myosin ATPase, and troponin inhibition, which produces energy, heat, increased oxygen demand, and sustained muscle contraction.⁹ The nature of MH without rigidity is unknown.

Unfortunately, there is no simple, accurate diagnostic test for MHS. A diagnosis of patient susceptibility must be based on a compilation of laboratory results modified by clinical judgment. Suspicions should be raised when musculoskeletal defects or a history of MH exist in the patient or relatives. Resting creatinine phosphokinase (CPK) and inorganic pyrophosphate levels should be determined when a questionable family history exists, and an anesthetic protocol should be instituted based on the presumption of an MH risk.

The presence of a musculoskeletal anomaly in-

creases the risk of MH (ptosis, strabismus, hernia, spontaneous dislocations of the joints, muscle weakness, atrophy of the skeletal muscles, and a tendency for severe skeletal muscle cramping).¹⁰ The relationship of muscle abnormalities to MH led to the suggestion that serum (CPK) levels may be elevated in patients at risk and could be used as an appropriate screening test. However, the reliability of CPK screening has been questioned since 30% of susceptible individuals have normal or inconsistently raised CPK values.¹¹ This interferes with CPK interpretation and gives rise to a false negative diagnosis of MHS. In addition, CPK values normally may be elevated in pregnancy, physical activity, alcoholism, and myocardial infarction,¹² giving rise to a false positive diagnosis of MHS. Although not an accurate test by itself, the CPK levels should be obtained in suspect individuals and results used in combination with other data.

Inorganic pyrophosphate level is another diagnostic screen for MH. It may be a more accurate screening device, although it is not syndrome-specific.¹³ When CPK and inorganic pyrophosphate values are elevated (normal values are determined by each laboratory) and a positive family history exists, the patient is considered MHS. When any of these findings are positive, and the others are normal, the patient still is considered clinically at risk for MH. Further testing would aid in diagnosis.

In vitro caffeine and halothane contracture tests also may be of diagnostic value.¹⁴ Muscle biopsy material from susceptible patients, when bathed in caffeine or halothane, develop sustained contractures which have a lowered threshold. These tests are specific for MH; however, they are utilized infrequently since they are invasive, time-consuming, and are available at a limited number of laboratories.

Clinical Features

In 75% of all cases of MH, muscle rigidity is the most consistent early symptom.^{1,2} Masseter muscle spasm — which produces mandibular trismus — readily is recognized, and, even though nonspecific for MH, the reaction must be considered and anesthesia terminated.¹⁵

Another early feature of MH is ventricular arrhythmia in the form of tachycardia, extrasystole, or bigeminal arrhythmia.⁵ It may be a result of an increase in serum potassium levels during muscle depolarization¹⁶ along with metabolic acidosis and accelerated oxygen demand.^{3,4,16}

During the onset of MH, increased muscle lactic acid formation results in metabolic acidosis and a decreased tissue and plasma pH. In addition, the hypermetabolic skeletal muscles produce large amounts

of CO₂, precipitating respiratory acidosis, and a compensatory tachypnea.⁵

One of the most prominent characteristics of MH is the onset of fever. The temperature may rise as rapidly as 1°F every 5 minutes due to heat production in the musculature.⁹ The higher the maximum temperature, the greater the mortality.¹⁰ In a small percentage of cases, fever does not accompany the other clinical features of the syndrome.

Cardiovascular complications of normothermic MH have been described. A defect may be found in cardiac muscle in addition to skeletal muscle.^{17,18} Examples may be anesthetic or nonanesthetic related and include atypical chest wall pain, unexplained cardiomyopathy, ventricular arrhythmia, and abnormal electrocardiograms.¹⁷

Dark venous blood in the operating field may signal an MH episode^{3,10} — it is a result of an increased oxygen demand. Elevated muscle metabolism increases oxygen consumption, precipitating decreased Po₂ levels.

Early laboratory findings are hyperphosphatemia, glucosemia, hypoxemia, hyperkalemia, hypermagnesemia, and hypercalcemia. Several hours later findings are hypocalcemia, hypophosphatemia, and myoglobinemia.⁵ Late complications include hemolysis, decerebration, impaired coagulation (platelets, fibrinogen, and Factor VIII are heat labile), muscle swelling, pulmonary edema,¹⁹ and acute renal shutdown resulting from myoglobinemia and precipitation of myoglobin in the renal tubules.¹⁶

Treatment of an MH Crisis

Emergency treatment during dental outpatient procedures should be implemented only after the development of clinical symptoms. A rising temperature of at least 1°C/15 min,⁴ muscle rigidity, and cardiac arrhythmia should be interpreted as a positive diagnosis for MH in an MHS patient.

Once a diagnosis of MH is made, immediate management of the crisis is imperative. Management protocol should be as follows:

1. Remove the causative agent immediately.²⁰ Cessation of general or local anesthesia may be adequate therapy.¹⁶ If removal of the triggering agent (anesthetic) does not attenuate the episode, direct treatment toward drug therapy and symptomatic care to reduce its severity.
2. Dantrolene should be administered after cessation of anesthesia. It is the drug of first choice, a muscle relaxant which blocks the mechanism coupling depolarization of the sarcolemma to Ca⁺⁺ release, thereby reducing intracellular Ca⁺⁺ levels.²¹ Side effects include: muscle weakness, drowsiness, dizziness, nausea, and hepatic dysfunction.¹

These reactions are minimized at recommended therapeutic doses. The effective IV dose is 1-2 mg/kg every 5-10 minutes to a total dose of 10 mg/kg. As dantrolene is metabolized, retriggering of MH may occur; therefore, administration should continue 12-24 hr.

3. Hyperventilate with 100% oxygen to increase blood oxygen saturation and to reduce the effects of respiratory acidosis. It decreases the elevated PCO₂ caused by the hypermetabolic musculature.^{3,20}
4. Implement cooling to lower the elevated body temperature. Cooling blankets, packing the patient in ice, and alcohol sponge baths accomplish surface cooling. Large blood flows in the axilla and groin may be packed with ice. Cooled saline can be administered IV or via gastric, peritoneal, rectal, urinary, or thorax lavage to lower core-body temperature.^{3,16,20} Terminate cooling when body temperature falls below 38.3°C to prevent hypothermia and subsequent cardiovascular problems.⁴
5. Administer IV sodium bicarbonate (2 meq/kg)²⁰ to reduce metabolic acidosis¹⁶ and the plasma potassium level. The potassium level returns to its intracellular position, reducing cardiac arrhythmia.

Clinical Report

A six-year-old white male was referred to the Dental Clinic at Milwaukee Children's Hospital (MCH) for a dental examination and treatment. A medical/dental history revealed that the patient had had several admissions at two years of age as a result of chest congestion, wheezing, and rales. Fluoroscopy and chest radiographs confirmed left lung hyperinflation and the presence of a foreign body. The patient had been taken to the operating room and, under halothane anesthesia, a diagnostic bronchoscopy was performed with subsequent removal of the foreign body (peanut). His 24-hour postoperative course was complicated by respiratory distress and a 106°F fever. He was intubated and placed on a respirator, at which time he had cardiopulmonary arrest. Following ordinary resuscitation procedures, a normal heart rate was reestablished in 5-10 min. Subsequent evaluation by a neurosurgeon showed that the child had marked seizure activity, secondary cerebral edema, and post-asphyxial brain damage. The child was discharged with a final diagnosis of mental-motor retardation.

Prior to dental treatment, a detailed family history was obtained from the parents. The history revealed the following: (1) a brother sustained an abnormal reaction to anesthesia at a dentist's office; (2) the maternal grandfather became febrile following local anesthesia for tooth extraction; and (3) a maternal uncle had an abnormal reaction to general anesthesia following leg amputation. The exact nature of the

postoperative complications was unclear in each case, but the family history combined with the child's past surgical complications certainly indicated possible MH.

Laboratory data obtained from the patient and immediate family deepened the concern (Table 1). Although the CPK value for the patient was near normal, paternal and sibling levels were high normal and, in one instance, exceeded normal. The entire family exhibited abnormally high inorganic pyrophosphate levels. A muscle biopsy and contracture test was not obtained due to parental refusal. However, based on the family history and the laboratory data available, a diagnosis of MHS was made. The dental treatment was tailored to the prevention of an MH episode and the child was scheduled for the operative procedures.

Although he had mental-motor retardation, cooperation was very good. Parameters monitored throughout the procedure included: (1) heart rate and rhythm; (2) axillary temperature; (3) respiratory rate; and (4) muscle tone. A total of 7.2 cc of .4% Ravocaine® and 2% Novocain® with Levophed® (1:30,000)^a, an ester-type local anesthetic, was used. Intravenous dantrolene (10 mg/kg) was prepared for use if a crisis ensued.

The operative procedures proceeded on a single quadrant basis to allow single quadrant anesthesia followed by observation. This allowed time for a gradual introduction of the anesthetic. Carious teeth were isolated with a rubber dam and amalgam restorations were placed in three maxillary and two mandibular teeth. An axillary temperature of 36°C was maintained throughout the procedure. The heart rate remained steady with a normal sinus rhythm. No evidence of increased metabolism or muscle tone was noted. After completion of the procedures the patient was observed in the clinic for approximately 2 hr, and then discharged to his home. The patient's mother was instructed to monitor his temperature at

TABLE 1. Laboratory Data From Child and Immediate Family

	<i>Creatinine Phosphokinase (CPK)</i>	<i>Inorganic Pyrophosphate (Solomon's technique)</i>
*Brother (1)	undetermined	104
Brother (2)	210	125
Sister	137	83
Mother	23	84
Father	144	129
Patient	67	129

*Previous abnormal reaction. CPK normals: 50-180 in males, 50-160 in females. Normal inorganic pyrophosphate: 63 ± 7 mg/dl in males and females.

^a Cook-Waite Laboratories, Inc. New York, NY.

least four times daily for the next two days and to observe skeletal muscle tone, breathing, and heart rate. No postoperative complications developed.

Discussion

Careful review of the family's anesthetic history and a subsequent finding of abnormal inorganic pyrophosphate levels in the patient and relatives revealed the patient's susceptibility to MH. He had undergone a previous general anesthetic (halothane) with a postoperative course consisting of cardiac arrest, respiratory distress, and elevated temperature (106°F). These reactions were highly suggestive of MH; therefore, the diagnosis of MHS was made.

Consideration was given to two types of premedication; one to alleviate stress and one to prevent an MH episode. Stress has been proven to be an etiologic factor only in swine; it may be a factor in humans. This patient was cooperative and outwardly calm; his base-line heart rate showed no indication of stress. Based on these factors and the recommendation of the anesthesia department, the child was not premedicated to alleviate stress.

Premedication with dantrolene is used by some in an effort to prevent an MH crisis from occurring. It is not the policy of the anesthesia department of MCH to use dantrolene to premedicate patients with confirmed MH. This policy was supported by an article published by Ruhland and Hinkle.²² They demonstrated that an MH reaction can occur, despite what was felt to be adequate pretreatment with dantrolene. In this case of susceptible but not confirmed MH, premedication with dantrolene was deemed inappropriate. Selection of an appropriate local anesthetic was critical. Amide-type local anesthetics may trigger Ca^{++} release from the sarcoplasmic reticulum, precipitating MH. Consequently, Ravocaine, an ester-type local anesthetic, was used. Procainamide, an ester, contributes to lowering intracellular Ca^{++} levels.^{4,19} Historically, it had been used to treat the syndrome, but since the inception of dantrolene, it no longer is the drug of first choice. The patient also was monitored during dental procedures requiring a local anesthetic for changes in metabolism. The parameters (as previously mentioned) were: body temperature, muscle tone, electrocardiogram, and respiration. If available, arterial blood gases and serum electrolytes are also desirable.²⁰ The dental work was accomplished slowly, one quadrant at a time, even though there was confidence that the local anesthetic would not precipitate an episode. Since the onset of an MH crisis is relatively rapid after introduction of a triggering agent, it was felt that a 2-hr postoperative waiting period was adequate to insure the patient's safety. Implementing proper preventive measures may not prevent the on-

set of MH. All materials necessary for treatment of a crisis should be available when rendering dental care to a patient at risk using either local or general anesthesia. Cooling blankets, ice, IV dantrolene (10 mg/kg), and sodium bicarbonate (2 meq/kg) were at the disposal of the dentist if an MH crisis had ensued.

Summary

MH is a genetically transmitted complication of general or local anesthesia with a high mortality rate of which dental practitioners should be aware. Prevention, the most effective way to reduce mortality, is accomplished by establishing patients at risk. Obtaining a detailed family history of past anesthesia complications is essential to prevention. Also, obtaining CPK and inorganic pyrophosphate levels for patients with questionable family histories of anesthesia-related death, fever, rigidity, or cardiac arrhythmia will help confirm a diagnosis of MHS. Inconsistencies may be observed between CPK, inorganic pyrophosphate, and family history; therefore, a clinical judgment is often necessary regarding the patient's susceptibility. When possible, muscle biopsy can aid in this judgment.

Early diagnosis and immediate emergency therapy will reduce mortality. During general or local anesthetic procedures a rising temperature of at least 1°C every 15 min, muscle rigidity, and/or cardiac arrhythmia should alert the dental practitioner to an imminent MH crisis. If a patient has been diagnosed as MHS, the proper armamentarium should be at one's disposal. Nitrous oxide may be used to reduce the stress of outpatient dental procedures. Belladonna, alkaloids, and phenothiazines should be replaced by safe preoperative medications such as meperidine (narcotic) and diazepam. Immediate treatment in a crisis situation should consist of: cessation of anesthetic agents; body cooling; and drug therapy consisting of IV dantrolene (10 mg/kg total dose), and administration of sodium bicarbonate (2 meq/kg).

The major concern in rendering dental treatment to these patients is doing it safely. The case presented demonstrated one method by which treatment can be rendered safely. Certainly, there are others. The authors neither encourage nor condemn out-patient management of these cases; they manage each patient individually in direct consultation with the anesthesia department of MCH.

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Quotable quote: observing child abuse

Evidence from this study and previous research by the investigators show that abusive mothers are inconsistent in interactions with their toddlers; they are at once more erratic in their punitiveness and more fearful of loss of control of their children. There is evidence that abusive mothers spend less time looking at their children and that when they look at them, fail to attend to them. Although larger group and time samples are necessary to confirm these initial and suggestive findings, further investigation and study of the interactive pattern that appears very early in the mother-child process should bring us closer to better treatment of child abuse.

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