Malignant hyperthermia (MH) is an uncommon and potentially life-threatening pharmacogenetic disorder. This abnormality in muscle metabolism can be triggered by a variety of agents (particularly general anesthetics and stress), resulting in a rapid heart rate increase, muscle rigidity, acidosis, temperature elevation, rhabdomyolysis, and renal failure. Immediate discontinuing of triggering agents, oxygenation, cooling, and dantrolene are necessary to treat an episode. MH-susceptible patients often indicate a positive family history of experiencing an adverse event during anesthesia. Few diagnostic tests are available to screen patients; the most accurate test is a skeletal muscle biopsy. MH-susceptible patients can undergo surgical procedures as necessary. Careful exploration of the medical history will allow the clinician to make the necessary modifications to treat and manage an episode expeditiously.

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First reported in 1900 as hyperpyrexia (an extreme elevation in body temperature as a reaction to anesthesia), malignant hyperthermia (MH) is characterized by a hypercatabolic reaction in the muscles of genetically susceptible individuals, induced by certain drugs or by physical or emotional stress. At the dental office, an MH-susceptible patient exposed to excessive stresses (such as pain, fear, or other triggering agents) may exhibit signs and symptoms of MH. Dentists must be aware of the disease's pathophysiology to prepare for, and hopefully prevent, an MH episode.

The estimated incidence of MH is 1:15,000 for children and 1:50,000 for adults. It occurs more frequently between the ages of 3 and 30 and is predominant in men. When MH was first recognized as a complication of anesthesia, its mortality rate was 70%; however, a 2003 article reported that diagnostic testing, increased awareness of the condition, and the use of appropriate treatment medications had lowered the mortality rate to approximately 5%.

MH has an autosomal dominant inheritance. The gene responsible for MH is located on the long arm of chromosome 19. More than 40 mutations have been found in the gene encoding for the skeletal muscle calcium release channel, known as the ryanodine receptor (RYR1). These mutations allow an abnormal response to triggering agents, resulting in MH.

A triggering agent has an abnormal effect on the skeletal muscles of a susceptible patient, as calcium ion concentration rises suddenly within the sarcoplasmic reticulum of skeletal muscles, resulting in muscle contraction. Subsequent rigidity indicates depletion of adenosine triphosphate (ATP) stores, which are crucial for the reuptake of calcium and reversing the condition. The disruption of cellular membranes allows potassium, calcium, creatine kinase, and myoglobin to enter extracellular fluid, resulting in metabolic acidosis, myoglobinuria, and disseminated intravascular coagulation (DIC). If untreated, MH could result in organ failure and death.

A review of the literature using MEDLINE reveals several cases of MH related to dental treatment. A 2006 article by Noguchi et al described a case of fatal MH in which a 12-year-old boy with cerebral palsy experienced extreme stress during the appointment. The patient was conscious during the appointment and was administered 0.5 mL of lidocaine prior to the extraction of a primary molar. Muscle spasms occurred shortly after the procedure. Dental anesthesiologists administered oxygen, intravenous diazepam, and diclofenac and transferred the patient to a general hospital. Despite additional treatment (including heparin, dantrolene, and blood transfusions), the patient's condition deteriorated over the next 13 days, resulting in rhabdomyolysis, DIC, and multiple organ failure.

In 2005, a 5-year-old boy experienced MH during a closed reduction procedure to treat a mandibular fracture. The boy had a history of uneventful general anesthesia and no family history of MH. Anesthesia was obtained using inhalational halothane and nitrous oxide; at that point, 20 mg of intravenous lidocaine was administered...
and nitrous oxide was discontinued. Surgeons administered 7.2 mL of 2% lidocaine locally and proceeded with archbar placement. The procedure was stopped once the symptoms of muscle rigidity, hypercarbia, tachypnea, and tachycardia were recognized. The incident was managed successfully by stopping the triggering agent, administering dantrolene, and applying cooling measures, including placing ice packs in the axillary and groin areas, switching to ice-cold IV fluids, and cold gastric lavage. The patient was transferred to a local hospital, where his symptoms resolved overnight.

Inada et al reported the case of an 11-year-old girl who underwent an alveolar cleft bone graft under general anesthesia, which resulted in persistent hyperthermia that lasted for five days postoperatively. The patient had undergone general anesthesia before without any complication. In this case, anesthesia was induced with the rapidly acting general anesthetic propofol followed by the non-depolarizing neuromuscular blocking agent vecuronium bromide and maintained with nitrous oxide. Local anesthesia at surgical sites was obtained using 16.5 mL of 1% lidocaine with 1:100,000 epinephrine and 25 mL of 1% lidocaine without epinephrine. Attempts to manage the hyperthermia with the NSAID diclofenac were unsuccessful; the episode was resolved by using oral dantrolene.

Monaghan and Hindle presented a case involving a 30-year-old woman with a history of successful general anesthesia who experienced MH one hour into an orthognathic surgical procedure. The surgeons first recognized tachycardia, warmth of the skin, and cyanotic appearance of the blood. The patient was managed successfully through cooling and the administration of dantrolene.

Nitrous oxide was implicated as the triggering agent in a 1985 report in which a 15-year-old boy with cerebral palsy and a history significant for MH experienced the condition during dental treatment, despite being premedicated with dantrolene when nitrous oxide was utilized. Anesthesia was uneventful at a subsequent appointment when the same premedication protocols were utilized and nitrous oxide was not administered.

Choung described a postoperative variant of MH termed human stress syndrome. Characterized by more subtle manifestations of MH without any extreme elevation in body temperature, human stress syndrome can result from exposure to physical or emotional stress outside a medical setting. Choung reported the case of a 17-year-old boy with no significant history who underwent orthognathic surgery. Postoperatively, his temperature was slightly elevated and an electrocardiogram (ECG) showed T-wave inversions. The patient complained only of generalized muscle soreness. His condition resolved...
the calcium, without success. The result is a breakdown of ATP, lactic acidosis, hypercarbia, and hyperthermia. The pathway that leads to MH is depicted in Figure 1.

Tachycardia is the most consistent early sign of MH. An unexplained increase in end-tidal carbon dioxide levels is a sensitive indicator of MH. Generalized erythema and an increased respiratory rate often are observed. Muscle rigidity develops (usually noted first in the masseter muscles) and will vary in terms of time of onset and severity, depending on the trigger agent. Biochemical changes include acidosis and an increase in levels of serum potassium, phosphate, and creatine phosphokinase (CPK) due to lactic acid production and muscle breakdown. Patients often will experience severe muscle soreness for several days after an MH crisis.

Several trigger agents (see Table 1) have been identified in MH. Trigger agents that are believed to be responsible for a majority of the cases include the depolarizing muscle relaxant succinylcholine and the volatile anesthetic agent halothane. Nitrous oxide and amide local anesthetics also have been implicated in MH. Though some believe nitrous oxide to be a trigger of MH, its frequent use as an anesthetic agent with susceptible patients would seem to discount this theory. As nitrous oxide has general anesthetic properties, it is appropriate to use it with caution for patients with personal or family history of MH. Contraindication for the use of amide local anesthetics is based on in vitro muscle contracture studies. Amide anesthetics have been demonstrated to cause muscle contraction, while ester anesthetics caused relaxation of muscle tissue, which inhibits contracture. Reviews of the literature have not demonstrated a clear link between amide anesthetics and MH and it generally is accepted that amide anesthetics are safe for MH-susceptible patients.

**Discussion**

It is essential for dentists to identify a patient's susceptibility to MH prior to treatment. MH may occur outside the operating room and result from factors unrelated to drugs, either emotional (excitement and stress) or physical (mild infections, vigorous exercise, and elevated environmental temperatures). Patients with a significant personal or family anesthetic history may be susceptible to MH. In addition, patients with a musculoskeletal disorder (such as myotonia congenita, myotonic dystrophy, joint hypermobility, ptosis, squint, thoracic kyphosis, lumbar lordosis, or scoliosis), with or without a history of MH, must be suspected for the condition.

MH is a genetic condition; as a result, a careful examination of the patient's medical history and family history (particularly where anesthesia is concerned) is revealing. In two of the case reports described above, details concerning significant family history were revealed only after the fact. Most episodes occur on the patient's first exposure to trigger agents; however, a personal history of uneventful general anesthesia does not rule out the possibility of an MH crisis occurring.

There are few simple diagnostic tests to identify an MH-susceptible patient. Muscle biopsies with contraction studies are needed to definitively diagnose MH. This procedure begins by taking a biopsy of approximately 2 g of muscle tissue from the vastus lateralis or medialis. The muscle tissue is exposed to caffeine or halothane in 48 hours; further questioning revealed that the patient experienced frequent muscle cramps during times of emotional stress.

**Pathophysiology of disease**

In MH-susceptible people, the RYR1 is in a more open resting state (greatly reducing the calcium ion bonding capacity) and the intracellular calcium ion release rate is three times greater than in a normal individual. The elevated cytoplasmic calcium concentration results in continued interaction between actin and myosin filaments, with sustained contracture. Biochemical pathways are activated to reuptake the calcium, without success. The result is a breakdown of ATP, lactic acidosis, hypercarbia, and hyperthermia. The pathway that leads to MH is depicted in Figure 1.

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and the force of muscle contracture is measured. This test has a current sensitivity of 97–99% and specificity of 85–90%. This test currently is available in eight medical centers in the U.S. and Canada.

Molecular genetic diagnostics hold great promise for a noninvasive diagnostic test that is highly reproducible and requires minimal biological material. As mutations in the gene encoding the calcium-release gene in skeletal muscle have been described as causal for MH, guidelines have been developed for clinical molecular testing.

Approximately 80% of family members who are susceptible to MH have significantly elevated CPK levels; a substantially higher correlation exists if myopathy is present.

Though not a specific indicator, CPK levels (combined with patient history and muscle biopsy) may help to identify MH-susceptible subjects.

Haas et al described a protocol for patient assessment that provides the clinician with an objective framework to evaluate an MH-susceptible patient based on medical history, diagnosis, and anticipated stress (see Table 2). Modifications to treatment can be made according to degree of susceptibility. An important element of this protocol is an evaluation of the stress the patient is likely to experience during the procedure. In a survey of patients who had experienced MH-like reactions during dental treatment, the presence of stress before the reaction—either because of anxiety or the procedure being performed—was a common theme.

Central to resolving an MH crisis is dantrolene sodium, a muscle relaxant that effectively blocks the release of calcium from the sarcoplasmic reticulum. Discontinuing triggering agents, combined with cooling measures and the administration of pure oxygen and dantrolene sodium can be effective in resolving an MH crisis. Management of a susceptible patient may involve the preoperative use of dantrolene. Once MH is resolved, symptoms such as tachycardia, rigidity, acidosis, and hyperthermia may return. Following a crisis, patients need to be monitored carefully in an intensive care setting, as 25% of cases have reported recrudescent MH within 48 hours of an episode.

Summary
MH is an uncommon and potentially life-threatening pharmacogenetic disorder. Characterized by a hypercatabolic reaction in muscle induced by certain drugs or by physical or emotional stress, MH can adversely affect the quality of and access to dental care. Patients with a history of MH may be denied treatment or receive care in an inappropriate setting. At the dental office, an MH-susceptible patient exposed to excessive stresses (such as pain and fear) may exhibit symptoms of MH. The dentist’s familiarity with the disease can enable MH-susceptible patients to receive dental treatment in a safe and reasonable manner.

Table 2. Patient assessment for MH

| A thorough medical history, to include family history with anesthesia, is essential. A positive diagnosis can be: |
| Unequivocally positive based on a positive muscle biopsy, or a confirmed reaction in the patient or immediate family member. |
| Equivocally positive based on a family history of unexplained death from general anesthesia, positive CPK blood test, or if patient has central core disease, Duchenne muscular dystrophy, myoadenylate deaminase deficiency, other myopathies, or heat stroke. |
| Consider degree of anticipated stress at appointment. A stressful appointment can be defined as: |
| Any treatment on an apprehensive patient. |
| A prolonged or extensive appointment. |
| A traumatic surgical procedure. |
| Based on degree of susceptibility to MH and stress, the clinician should make necessary modifications to treatment. |

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