Malignant hyperthermia (MH) is a potentially fatal clinical syndrome that classically presents during the administration of potent, volatile anesthetic agents and depolarizing muscle relaxants. MH may also occur in susceptible individuals under extreme stress from heat or exercise. The syndrome was first described in 1960 by Denborough and colleagues as an inherited disorder of the skeletal muscle. They characterized MH as a hypermetabolic state with skeletal muscle rigidity that occurs after the administration of general anesthetics, and that arises frequently, but not exclusively, in children. If recognized early, the condition can be treated by administering dantrolene, a muscle relaxant. Additional therapies include cooling and hyperventilation of the patient. If treatment is not given promptly, the patient may suffer from rhabdomyolysis secondary to sustained muscle contraction postoperatively. A disruption of muscle cell membrane allows leakage of myoglobin and creatine kinase into the plasma, which can lead to myoglobinuria. Muscle cell necrosis may occur, causing renal failure and even cardiac arrest. A decreased range of motion, weakness, and severe muscle pain may also be experienced.

MH is a rare disorder with an incidence ranging from 1 in 15,000 children to 1 in 50,000 adults who received triggering agents (eg, succinylcholine and inhalational anesthetics).

Older children and adults younger than 30 are the most likely to be affected. Geriatric patients and children younger than 3 have a lower incidence.

The Presentation of MH

Genetics and Triggering Agents

MH normally occurs when susceptible patients are exposed to a triggering agent. MH can be avoided when an extensive personal or family history of the patient has indicated a risk for the disease, a definitive diagnosis has been made, or a high index of suspicion has alerted healthcare workers. Studies indicate that MH displays heterogeneity with autosomal dominant inheritance, reduced penetrance, and variable expressivity. Rykyvaldione, a plant alkaloid, has been shown to bind calcium release channels in the sarcoplasmic reticulum. The ryanodine receptor is abnormal in patients with MH and results in the inappropriate release of Ca²⁺ in such individuals. Evidence suggests that chromosomes 17 and 19 may play a role in the genetic abnormalities of this heterogeneous, polygenic disorder.

Mutations in the ryanodine receptor type 1 (RYR1) gene commonly occur in 3 mutational “hot spots.” Recently, see Lesson 248 page 50
Tachycardia, tachypnea, hyperthermia, Local anesthetics
Benzodiazepines

Figure 1. The clinical presentation of the patient with MH.

Table 1. Agents Classified as Triggering
And Nontriggering for MH

<table>
<thead>
<tr>
<th>Triggering</th>
<th>Nontriggering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potent inhalation agents</td>
<td>Nondepolarizing muscle relaxants</td>
</tr>
<tr>
<td>Halothane</td>
<td>Barbiturates</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>Local anesthetics</td>
</tr>
<tr>
<td>Desflurane</td>
<td>Propofol</td>
</tr>
<tr>
<td>Succinylcholine</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Signs and Presentation of MH

<table>
<thead>
<tr>
<th>More specific</th>
<th>Less specific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercarbia, muscle rigidity, rhabdomyolysis</td>
<td>Tachycardia, tachypnea, hyperthermia, hyperkalemia, hypocalcemia</td>
</tr>
</tbody>
</table>

Table 3. Myopathies That Predispose to MH

<table>
<thead>
<tr>
<th>Central core disease</th>
<th>Hypokalemic periodic paralysis</th>
<th>King-Denborough syndrome</th>
<th>Muscular dystrophy</th>
</tr>
</thead>
</table>

Lesson 248 continued from page 49

however, Samboughin and colleagues were able to identify 9 previously unknown RYR1 mutations by using denaturing high-performance liquid chromatography (DHPLC) to analyze RNA samples from the sarcoplasmic reticulum of patients with, and susceptible to, MH. They concluded that their approach increased the rate of detection of mutations up to 70%—signifi-
cantly higher than the approximately 25% that has been reported. Furthermore, their study suggested that: RYR1 mutations may be present in up to 70% of patients diagnosed with MH or in those with a predisposition to the disease (MH-susceptible); mutations may be found outside the original hot spots; and DHPLC may be useful for future screening.

Common triggering agents for MH include succinylcholine and potent inhalation anesthetics such as halothane, sevoflu-
rame, and desflurane. Drugs that do not trigger MH include nondepolarizing muscle relaxants, barbiturates, local anes-
ethetics, propofol, ketamine, benzodiazepines, and nitrous oxide (Table 1).14

Intraoperative Clinical Presentation

Signs of MH include tachycardia, tachypnea, hyperther-
mia, generalized muscle rigidity, and acidosis. The most sen-
sitive and specific sign, however, is a rising end-tidal carbon dioxide (ETCO2) concentration (Table 2) in the background of hyperventilation or constant minute ventilation.15 The result is a mixed metabolic and respiratory acidosis as a result of anaerobic and aerobic metabolism. There is an increase in sympathetic tone and heart rate. The combination of sympa-
thetic drive and peripheral vasodilation secondary to tissue edema, muscle edema, consumptive coagulopathy, neurolog-
isms. Microscopically, the muscle cells exhibit a central area of necrosis, giving the appearance of a cell with a “cored out” center. Causal mutations associated with this disorder—found on the ryanodine receptor gene—result in abnormal Ca2+
homeostasis in skeletal muscle.36

Multiple conditions mimic MH in presentation (Table 4). A careful examination of the patient can help differentiate these. For example, postsurgery sepsis in the patient presenting with fever, tachycardia, tachypnea, and acidosis resembles the presentation of MH. In postsurgery sepsis, the increase in ETCO2 is caused by hypermetabolism, as is seen in MH. To distinguish sepsis from MH, the clinical setting must be exam-
ined, as well as the patient’s response to antibiotics.37 Another cause of hypermetabolism is thyrotoxicosis. Although rare, the patient with elevated thyroid hormone can present with tachycardia, tachypnea, and hyperthermia, although muscle rigidity is absent.25

Differential Diagnosis

Multiple conditions mimic MH in presentation. A careful examination of the patient can help differentiate these. For example, postsurgery sepsis in the patient presenting with fever, tachycardia, tachypnea, and acidosis resembles the presentation of MH. In postsurgery sepsis, the increase in ETCO2 is caused by hypermetabolism, as is seen in MH. To distinguish sepsis from MH, the clinical setting must be exam-
ined, as well as the patient’s response to antibiotics.37

Pathophysiology and Molecular Biology

Advances in molecular genetics have shed light on under-
standing the pathophysiologic mechanism of MH.24 Studies indicate that triggering agents lead to an uninhibited release of calcium from the sarcoplasmic reticulum of skeletal muscle. The critical initial event is a sudden rise in myoplas-
mic calcium, with a peak rate of intracellular calcium release that is up to 3 times greater than normal individuals.

Ultimately, the release of extra calcium results in a sus-
tained muscle contracture and the increased use of adeno-
sine triphosphate. In addition, the increase in aerobic metabolism elevates carbon dioxide levels, so that both respi-
atory and metabolic acidosis are common findings. Intracel-
lar high-energy phosphate degradation is hypothesized to result in the leakage of potassium, calcium, myoglobin, and creatine kinase into the circulation, secondary to a loss of sarcolemmal integrity.23 Furthermore, biochemical studies have revealed that muscles of patients with MH have a lower threshold for excitation—known as a potassium ion shift.23,24 As a result of these findings, the pathophysiology of MH is now regarded as an exaggerated muscular response to calci-
mum, rather than an exceptional pathology.25

Predisposing Disorders

Central core disease, hypokalemic periodic paralysis, and King-Denborough syndrome are myopathies associated with MH susceptibility.24 Central core disease, characterized by hypotonia and progressive muscle weakness, is inherited via either autosomal dominant or autosomal recessive mecha-

isms. Microscopically, the muscle cells exhibit a central area of necrosis, giving the appearance of a cell with a “cored out” center. Causal mutations associated with this disorder—found on the ryanodine receptor gene—result in abnormal Ca2+
homeostasis in skeletal muscle.36

Another cause of hypermetabolism is thyrotoxicosis. Although rare, the patient with elevated thyroid hormone can present with tachycardia, tachypnea, and hyperthermia, although muscle rigidity is absent.25 Myopathies such as Duchenne’s dystrophy and Becker’s muscular dystrophy are characterized by an absence or alteration of the dystrophin protein. The administration of succinylcholine or other MH-
triggering drugs can lead to life-threatening hyperkalemia and muscle rigidity.30

Table 4. Multiple Conditions Mimic MH

<table>
<thead>
<tr>
<th>Multiple Conditions Mimic MH</th>
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</thead>
<tbody>
<tr>
<td>Hypermetabolism</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
</tbody>
</table>

symptoms in this group of patients.35

Myotonia, characterized by prolonged muscle contraction, can mimic MH. Patients with the classic form, myotonic dystrophy—characterized by extended and intense muscle rigidity, may respond to succinylcholine administration. The hypermetabolism associated with MH, however, is not observed in these patients.36

In patients suffering from neuroleptic malignant syndrome, tachycardia, fever, muscle rigidity, acidosis, and elevated creatine kinase levels are found. In such patients, however, a history of the ingestion of neuroleptic medication (e.g., phenothiazines, haloperidol, or antipsychotics) is established. The administration of benzodiazepines or bromocriptine is efficacious in these patients.37,38

In cases involving lengthy surgery of peripheral, localized parts of the body, such as of the hand or foot, aggressive warming may be used to prevent hypothermia. Unfortunately, this treatment can lead to severe iatrogenic hyperthermia. Ineffective vasodilatation in these patients results from draping, and heat dissipation becomes suboptimal. Body temperature may rise considerably, and therefore temperature should be monitored in patients undergoing surgery that lasts a significant length of time.38

Head trauma cases may present with similarities to MH. Injury to the brain can cause hyperthermia, hypermetabolism, and tachycardia via several mechanisms, including increased metabolic demand, catecholamine release, hypothalamic injury, inflammatory changes, lipid peroxidation, and cell death. Other signs and symptoms of brain injury are an altered level of consciousness, dystonia, hypertension, tachypnea, agitation, and diaphoresis.39

**Laboratory Diagnosis**

In 1977, Kalow et al exposed biopsied muscle tissue to gradual increments of caffeine. They observed a leftward shift of the dose-response curve when using muscle taken from patients who had reported episodes of MH. Earlier, Ellis and colleagues had described how muscle contracted in response to different concentrations of halothane in vitro. Today, the in vitro contracture test (IVCT) is the gold standard for diagnosing MH.34,36

Patients with a family history of MH, or who develop unexplained hypercarbia or exhibit peripheric rhabdomyolysis, are suitable candidates for biopsy. The IVCT requires approximately 2 g of muscle excised from either the vastus lateralis or vastus medialis muscle. Subsequently, the muscle is dissected into longitudinal strips, sutured at both ends, and placed into baths. One end of the strip is attached to a force transducer while the other is attached to an immobilized hook. The contractile response of the muscle is measured against incremental doses of caffeine and halothane. A contracture of 0.7 g or greater with halothane or 0.3 g with caffeine is considered an abnormal (positive) response and is diagnostic for MH. Presently, this standardized test approach has 99% sensitivity and up to 90% specificity. European, Japanese, and North American protocols differ by varying caffeine and halothane concentrations, and, in addition, use different diagnostic thresholds.34,36

To enhance the specificity of the IVCT, new diagnostic agents such as ryanodina (a potent ligand of the ryanodine receptor) or another compound, 4-chloro-m-cresol, is used. Another compound, 4-chloro-m-cresol, is a substitute or supplement for caffeine in the IVCT. 4-Chloro-m-cresol acts similarly to caffeine by releasing Ca2+ through the ryanodine receptor, but shows a higher potency than caffeine. 4-Chloro-m-cresol may exert its effect via a different binding site than does caffeine. Patients are diagnosed as either MH-susceptible (muscle reacts to halothane and caffeine challenge) or MH-normal (muscle demonstrates no reaction to halothane and caffeine challenge) according to the standardized protocols developed by the European Malignant Hyperthermia Group. Although 4-chloro-m-cresol is used to increase the accuracy of the IVCT, recent research suggests that the compound is not superior to caffeine in discriminating between MH-normal and MH-susceptible cells in other minimally invasive experiments, such as calcium imaging tests.34

Contracture-inducing substances that have been studied in swine may direct future research on MH. In a recent study by Fiege and colleagues, enoximone, a type-III phosphodiesterase (PDE-III) inhibitor, stimulated marked contracture in MH-susceptible humans as well as swine. To determine whether the contraction was caused by PDE-III inhibition or by a substance-specific effect, studies on swine were also performed with inamrinone, another PDE-III inhibitor. The administration of inamrinone resulted in marked contractions, suggesting that PDE-III and the cyclic adenosine monophosphate system may be involved in MH pathophysiology; these findings may lead to additional test protocols in the future.39

According to the Web site for the Malignant Hyperthermia Association of the United States (MHAUS), www.mhaus.org, there are currently 6 centers in the United States and 2 in Canada that comply with the standardized protocols for muscle biopsy testing for MH. Presently, muscle biopsy centers do not pay for patients’ travel expenses, and reimbursement for travel and expenses varies from one insurance company to the next.

In the future, molecular genetic diagnostics might become the standard methodology for MH testing. Such tests are specific, highly reproducible, and minimally invasive. Furthermore, only a small amount of biologic material is required, although currently these tests are relatively expensive.36 Molecular genetic testing may also eliminate false-negative diagnoses of MH, which will help prevent unnecessary complications and surprises in the operating room during anesthesia. European guidelines for genetic testing have already been incorporated as a supplement to the IVCT protocol (Figure 2).34,36

Other tests for MH that have been developed involve the measurement of creatine kinase, creatine phosphate, adenine triphosphate, and pH; nuclear magnetic resonance spectroscopy; lymphocyte tests; and cultured muscle cells.36,37

<table>
<thead>
<tr>
<th>Table 4. Differential Diagnosis</th>
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<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
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<tr>
<td>Postsurgery sepsis</td>
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<tr>
<td>Thyrotoxicosis</td>
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<tr>
<td>Duchenne’s dystrophy and Becker’s muscular dystrophy</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
</tr>
<tr>
<td>Neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>Iatrogenic hyperthermia</td>
</tr>
<tr>
<td>Head trauma</td>
</tr>
</tbody>
</table>

**Figure 2. Protocol for genetic testing.**39

IVCT, in vitro contracture test; MH, malignant hyperthermia; MHN, malignant hyperthermia–normal; MHS, malignant hyperthermia–susceptible

CK, creatine kinase

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December 2005

Anesthesiology News
Table 5. Treatment of the Patient With MH

<table>
<thead>
<tr>
<th>Treatment and Management of MH</th>
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<tbody>
<tr>
<td>Although MH is a life-threatening disease, swift and proper treatment can prevent complications. The first step in preventing complications is the availability of an MH kit. MHAUS recommends that each kit contain 36 vials of dantrolene, sterile water without bacteriostatic agent for injection, and bicarbonate. Each 70-ml vial contains 20 mg of dantrolene and 3 g of mannitol. By directly affecting the contractile response of muscle and excitation-contraction coupling, the mixture results in skeletal muscle relaxation. Side effects may include nausea and vomiting, pain at the injection site, and weakness. Dantrolene sodium is specific to skeletal muscle and, therefore, does not create problems with smooth or cardiac muscle. It reverses the hypermetabolic state by dissociating the excitation-contraction coupling by blocking calcium release from the sarcoplasmic reticulum. With IV administration, the effects of dantrolene are noticed within 2 to 3 minutes; its average half-life is between 5 and 8 hours, but can extend to 12 hours in some patients with MH. MHAUS has developed a management protocol that recommends a loading dose of 2.5 mg/kg of dantrolene via a large-bore needle. If needed, incremental doses of up to 10 mg/kg may be administered. Dantrolene is continued at 1 mg/kg intravenously every 6 hours for the next 48 to 72 hours after the episode. Because the dantrolene preparation contains 3 g of the osmotic diuretic mannitol, urinary output must be monitored by means of a urinary catheter. In order to prevent renal failure, urinary output should be &gt;30 mL per hour. Although dantrolene is not recommended for prophylaxis, if the anesthesiologist chooses to use it for this purpose, 2.5 mg/kg intravenously, 30 minutes before anesthesia, is suggested. As soon as an episode of MH is recognized, the administration of all volatile inhalational anesthetics and succinylcholine should be discontinued immediately. Management of the patient should include hyperventilation with high-flow 100% oxygen as dantrolene is prepared and dispensed. Cooling blankets or ice packs should be used concurrently to help control hyperthermia. MHAUS provides consultation to clinicians via a hotline telephone number: (800) MH-HYPER (8800) 644-9737. Although cardiac arrhythmia generally abates when acidosis and hyperkalemia are brought under control, it may persist. In such cases, standard antiarrhythmic agents can be used, but calcium channel blockers are contraindicated because they can worsen the hyperkalemic condition and lead to cardiac collapse. Agents for the treatment of hyperkalemia include bicarbonate, I.V. glucose, and insulin. In addition, ETCO2 arterial blood gases, potassium, calcium, urine output, and blood clotting values must be strictly monitored. After an episode of MH, the patient should be carefully observed postoperatively for recurrence. A minimum of 36 hours of surveillance in the intensive care unit is recommend. The I.V. administration of 1 mg/kg dantrolene every 6 hours for 24 to 48 hours may also help prevent a recurrence. Arterial blood gases, creatine kinase, potassium, calcium, and myoglobin levels, in addition to body temperature and blood clotting, should all be monitored until normal values are obtained (Table 5).</td>
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</tbody>
</table>

Prevention

Taking preventive measures against MH should be emphasized because the onset of hyperthermia is usually unexpected and potentially catastrophic. Obtaining a thorough anesthetic history from the patient, which takes into account family members who have had MH, is the first step. Family relatives identified as MH-susceptible should not be given triggering agents. For these individuals, testing for MH is recommended. Obtaining medical records for relatives is often possible if the patient is seen in an outpatient facility before surgery. Myotonia in a patient is a strong indication against the use of succinylcholine. Moreover, patients with predisposing disorders such as central core disease and muscular dystrophy should not be given triggering agents (Table 3). Intraoperative monitoring of the patient’s core temperature may help detect an ensuing episode of MH. |

Management of the Case

The intubated patient arrived in the operating room and monitors for vital signs were applied. The patient’s vital signs were stable: heart rate, 85 beats per minute; blood pressure, 110/60 mm Hg; SpO2, 100% on a circle breathing mask. The patient was administered 5 mg/kg of fentanyl, isoflurane 1.1%, 1.0 L per minute of oxygen, and 1.0 L per minute of air, then paralyzed with additional vecuronium, 0.04 mg/kg. The ventilator was set at 400 mL (8 mL/kg); a rate of 12, I:E, 1:2; and inspired O2, approximately 0.55. Approximately 15 to 20 minutes into the case, the patient’s heart rate began to increase. Fluid administration and the concentration of the volatile agent were increased. The patient’s blood pressure was maintained at about 110/60 mm Hg, and additional fentanyl was administered. For the next 10 to 15 minutes, tachycardia gradually became more pronounced (115-125 beats per minute) and blood pressure decreased slightly. The patient received 2 additional liters of lactated Ringer’s fluid–delivered through both peripheral lines with a pressure bag. Her heart rate continued to climb (135-155 beats per minute), her temperature rose to 103.8°F, her blood pressure continued to fall, and at that time, it was first noticed that CO2 concentration was rising (45-55). The ventilator was adjusted by initially increasing the rate, and then increasing the rate and volume. For 5 to 10 minutes, other causes of the patient’s intraoperative tachycardia were investigated and ruled out. Light anesthesia, hypovolemia, hypoxia, hypercarbia, pulmonary embolism, and sepsis/fever. The ETCO2 value did not decrease in response to the increased ventilator settings, but persistently rose. The surgeons were notified to finish the procedure as soon as possible, and the anesthetic agent was turned off. Over the next 20 to 30 minutes, the ventilator rate was decreased to 10 respirations per minute, and delivery of 100% O2 was initiated. The circuit was flushed and an MH cart was obtained. The patient was packed in ice from groin to axillae and behind the neck. Central and arterial cannulae were placed and a total of 140 mg of dantrolene, 25 g of mannitol, and 20 mg of furosemide were administered. Propofol and fentanyl infusions were started and a bolus dose of scopolamine delivered. The tachycardia continued but at a slower rate (100-110 bpm), and then normalized 1 hour after the dantrolene was administered. The patient’s blood pressure returned to normal 20 to 30 minutes after treatment began and her temperature fell to 96.8°F after 1 hour. The patient was transferred to the surgical intensive care unit on a dantrolene regimen of 1 mg/kg every 6 hours for 24 hours. The patient’s family was informed in detail of the complications and the implications of the diagnosis. A letter was sent to the family after discharge of the patient on day 10. Subsequent surgeries on the patient were performed with a total I.V. anesthetic technique and there were no further complications. |

Conclusion

Although MH is potentially fatal, morbidity and mortality can be reduced when it is recognized early. A thorough medical and family history is at the core of prevention, with laboratory findings being confirmatory of the disease. Many clinical anesthesiologists will simply decide to avoid the use of triggering agents after hearing a family history described in the preoperative history. Researchers are developing newer testing modalities that stem from the gold-standard IVCT. In a situation where MH presents unexpectedly, dantrolene should be administered immediately, and the triggering anesthetic discontinued. A national MH hotline is available 24 hours per day to provide experienced advice should a case arise. Increased awareness and early recognition of MH have helped decrease the mortality and morbidity of this disease over the last 20 years. With new improvements in laboratory diagnostics, it may decline further.
Lesson 248: PreAnesthetic Assessment of the Patient With Malignant Hyperthermia

Post-test

1. Within what time period are the effects of dantrolene noticed after I.V. administration?
   a. 30 seconds
   b. 2 to 3 minutes
   c. Depends on the triggering agent
   d. >10 minutes

2. Which of the following is not a trigger for malignant hyperthermia (MH)?
   a. Propofol
   b. Desflurane
   c. Halothane
   d. Succinylcholine

3. MH in humans:
   a. may be inherited as an X-linked trait
   b. can be caused by an abnormality of chromosome 16
   c. causes fever and rigidity by definition
   d. can present with spasm of the masseter muscle

4. The administration of dantrolene:
   a. blocks potassium uptake
   b. blocks calcium release from the sarcoplasmic reticulum
   c. is commonly used in the prevention of MH
d. all of the above

5. Characteristics of MH include all of the following except:
   a. autosomal dominant transmission
   b. triggering by local anesthetic agents
c. an association with central core myopathy
d. improved survival after administration of dantrolene

6. Which of the following is true regarding MH?
   a. Unexplained tachycardia is common.
b. Bilateral strabismus
c. Myotonia
   d. History of heat stroke

7. Which of the following is most clearly associated with MH?
   a. Hypercarbia
   b. Bilateral strabismus
c. Central core disease
   d. History of heat stroke

8. Which of the following is not a sign of MH?
   a. Hypercarbia
   b. Rhabdomyolysis (elevated creatine kinase)
c. Muscle rigidity
d. Decreased oxygen saturation

9. Which of the following is not a sign of MH?
   a. Hypercarbia
   b. Bilateral strabismus
c. Central core disease
   d. History of heat stroke

10. In vitro contracture testing is enhanced by the addition of:
   a. 4-chloro-m-cresol
   b. Caffeine
c. Dantrolene
d. Succinylcholine

References