Malignant Hyperthermia
Last updated on 08/01/2012, previously 11/13/2007.

Contributors:
Ned Patterson DVM, PhD, DACVIM (SAIM)
Linda Shell, DVM, DACVIM (Neurology)

Synonyms:
Canine Stress Syndrome

Disease description:
Malignant hyperthermia (MH) is the rapid, exaggerated, uncontrollable elevation of body temperature, in animals susceptible to the syndrome, induced by an external stimuli. The external stimuli may be psychological stress (excitement, fighting for dominance, etc.), environmental stress (extreme heat, increased activity), other stresses, anesthetic agents (halothane), depolarizing muscle relaxants (succinylcholine), and possibly toxicants. It has been described in dogs, humans, pigs, horses and cats.

Genetic basis/mode of inheritance: A c.1640T>C mutation in the RYR1 gene which is autosomal dominant has been identified in a colony of dogs, but has not been yet found in any dogs in the general dog population.

PATHOPHYSIOLOGY

The major calcium release channel in the skeletal muscle sarcoplasmic reticulum membrane is the ryanodine receptor (RYRI). The gene that encodes this receptor has been cloned and research has linked gene mutations to MH. The physiologic mechanism of MH is believed to be abnormal calcium hemostasis (specifically calcium release) that results in prolonged increases in calcium concentrations and subsequently prolonged muscle contractions. This results in extreme elevation of body temperature sometimes as high as 110 F.

Severe hyperthermia results in increased metabolic activity and unreplenished oxygen consumption. This will cause cell death and can result in multiple organ failure and disseminated intravascular coagulation.
**CLINICAL SIGNS**

Clinical signs may include extreme hyperthermia, muscle fasciculations or spasms, tachycardia, tachypnea, hyperventilation, blood pressure fluctuations, metabolic acidosis and respiratory alkalosis, and cardiac arrest. The hypermetabolic state can produce hypercarbia, rhabdomyolysis, generalized skeletal muscle contracture, cardiac dysrhythmia, renal failure, disseminated intravascular coagulation, and death.

**DIAGNOSIS**

Diagnosis of MH and its related syndromes is often problematic. The neurologic and physical examinations are usually within normal parameters.

**In vitro contracture test (IVCT):** This is the standard assay used to confirm a diagnosis of MH in people after an anesthetic triggered episode, and to survey families for MH susceptible individuals. (Kalow et. al., Lancet 1970). A muscle biopsy sample is surgically removed from the patient and the degree to which it contracts when exposed to caffeine or halothane is compared to normal muscle. The assay has considerable variability, is invasive, and is difficult to perform, but does identify both heterozygotes and homozygotes. IVCT can also be performed in dogs, but few in any labs are currently able to perform this test on a commercial level.

**Halothane exposure:** Diagnosis can be based on halothane exposure, but this method is less than ideal, as an adverse and serious reaction in a positive patient will likely result in death. This approach is only appropriate if dantrolene (see treatment section) is available to reverse the effects before significant damage is done.

**Erythrocyte fragility testing:** There is a defect in the erythrocytes of MH dogs and swine such that they have increased susceptibility to hydrogen peroxide-induced hemolysis. This is thought to be due to partial deficiencies of multiple antioxidant stem enzymes, such as glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, and others. However, few commercial facilities are available that routinely test erythrocyte fragility.

**Disease description in this species:**
MH has also been called Canine Stress Syndrome (CSS). Although still under investigation, it is known that at least some dogs inherit this condition as an autosomal dominant trait, resulting in mutations in the calcium release channel of the sarcoplasmic reticulum, also known as the ryanodine receptor (RYR1). The mutated RYR1 causes abnormal calcium homeostasis that results in prolonged increases in calcium concentrations and muscle contraction. The prolonged and profound muscle contraction then causes the rapid depletion of ATP, breakdown of muscle energy stores, and a lactic acidosis.
Dogs were first clinically diagnosed with this disease in 1973. Some dogs were only identified with this condition after the administration of halothane anesthesia. These animals developed hypercarbia and increased carbon dioxide production within 10 minutes of induction. Tachycardia and hyperthermia followed usually within the first hour of anesthesia. Death would result if anesthesia was not discontinued. It is still possible that there continue to be rare events in dogs with inhalant anesthetics, but they are infrequently recognized in dogs, since dogs may develop arrhythmias from MH and die before their temperature elevates dramatically. There are not any documented cases of dogs having true malignant hyperthermia causing a stress syndrome similar to pigs with autosomal recessive mutations in the RYR1 gene causing porcine stress syndrome.

**Etiology:**
Amide local anesthetics  
Anesthetic agents  
Genetic, hereditary  
Hypercalcemia  
Hypercarbia, increased CO  
Hypoxemia  
Idiopathic, unknown  
Infection  
Inhalants  
Ketamine  
Muscle relaxants  
Muscular exertion  
Succinylcholine hydrochloride  
Sympathomimetics  
Trauma

**Breed predilection:**
Border collie  
Doberman pinscher  
German shepherd X Doberman pinscher  
Greyhound  
Labrador retriever  
Pointer  
Saint Bernard  
Spaniel  
Springer spaniel

**Clinical findings:**
ANOREXIA, HYPOREXIA  
Cachexia, weight loss  
Dehydration  
FEVER  
Malaise  
Oliguria
Polydipsia
TACHYCARDIA
Tachypnea, Hyperpnea, Hyperventilation
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**Diagnostic procedures:**
- Blood bicarbonate of EDTA blood
- Serum chemistry
- Urinalysis and Urine Sedimentation
- Blood pH on EDTA blood
- Blood pressure measurement
- Electrocardiography
  - Halothane-succinylcholine challenge exposure test
  - Caffeine induced contracture test on muscle biopsies
  - RBC fragility test

**Diagnostic results:**
- Blood bicarbonate decreased, metabolic acidosis
- Creatine kinase (CK, CPK) increased
- Urine specific gravity increased
- Respiratory alkalosis
- Blood pressure unstable
- ELECTROCARDIOGRAPH ABNORMAL
  - Supraventricular tachycardia
  - Abnormal contraction response halothane succinyl choline change
  - Increased sensitivity to caffeine induced contracture test
  - Increased fragility RBC

**Treatment/Management/Prevention:**
**SPECIFIC**

1) Dantrolene: 0.2 to 3.0 mg/kg IV. This skeletal muscle relaxant has been shown to be very effective in treating an acute attack. The prophylactic benefit of daily administration of dantrolene has not been determined.

2) The mainstay of therapy is aimed at avoiding stressful situations and maintaining a quiet, cool environment.

**Human Disease Homolog:** Malignant Hyperthermia. Online Mendelian Inheritance in Man (OMIM)# 145600  MIM# 180901.

**Genetic Testing:** Contact the canine and equine genetics lab at the University of Minnesota College of Veterinary Medicine for possible genetic testing on a case by case basis. [http://www.cvm.umn.edu/vbs/faculty/Mickelson/lab/home.html](http://www.cvm.umn.edu/vbs/faculty/Mickelson/lab/home.html)

**References:**