

Canine Stress Syndrome

Formerly known as Canine Malignant Hyperthermia (CMH), Canine Stress Syndrome (CSS) is a hereditary disorder characterized by sudden muscle tremors, muscle rigidity, or seizures. With a potential for being mislabeled as idiopathic epilepsy or muscle dystrophy, CSS is now recognized as a prevalent disorder in the Labrador retriever with episodes being triggered by stress stimuli including but not limited to exercise, routine handling, feeding, fasting, vaccine administration, etc.

The following article explores this hyper-metabolic disorder, which researchers compare to Malignant Hyperthermia (MH) occurring in humans and pigs, and explains what is currently understood as the underlying cause for this potentially fatal disorder.

What causes CSS?

To understand the physiological condition that results in episodes of CSS it is first necessary to provide a brief overview of normal muscle structure and function.

There are three classes of muscles: smooth, cardiac, and striated. The smooth muscles are under involuntary control by the central nervous system and therefore, their function does not require conscious control. Smooth muscles surround internal organs such as the intestines, gall bladder, and large blood vessels. Contractions of these muscles function primarily to move food along the digestive tract and control the diameter of blood vessels.

Cardiac muscles are specialized for continuous involuntary contractions responsible for pumping of blood.

Striated muscles connect the bones in the arms, legs and spine and are used for voluntary, coordinated activity such as walking, head movement, etc. The striated muscles are those that are affected in CSS.

Striated muscle cells are called myofibers. Each myofiber is long and cylindrical and contains many bundles of filaments called myofibrils. The myofibrils are in turn constructed of repeating segments of thick filaments (myosin) and thin filaments (actin). Each of these segments makes up a sarcomere (a unit of contraction). Muscle contraction occurs when the thick and thin filaments slide past each other. Movement of the filaments and resulting contraction of the muscle is energy dependent. Each myofibril is surrounded by mitochondria (cellular organelles that generate cellular energy) and granules of glycogen (stored sugars) which are used to generate energy in the form of high-energy phosphates (i.e. adenosine triphosphate [ATP]) that can be utilized as fuel for cellular processes. If a muscle is depleted of energy sources such as ATP or creatine phosphate, it becomes stiff and can no longer be extended (a condition known as "rigor"). When this condition occurs, the actin and myosin filaments are tightly crosslinked together so that the thick and thin filaments cannot slide past each other. Only ATP (energy) replenishment (through breakdown of sugar stores or import of sugar from the blood) will weaken the myosin-actin bond and release the contracted muscles.

The signaling of muscle contraction is dependent upon calcium levels. Surrounding each myofiber is a network of membrane vesicles called the sarcoplasmic reticulum (SR). The SR is a reservoir for calcium (Ca^{++}) and contains Ca^{++} binding proteins that store large amounts of Ca^{++} . During movement, stimulation of muscle causes Ca^{++} to be released from the SR under control of the "ryanodine receptor calcium release channel" (Ry1). Release of Ca^{++} triggers the motion of the

actin/myosin fibers resulting in muscle contraction. Continued stimulation of the muscle retains the high levels of Ca^{++} . When stimulation ceases, Ca^{++} is pumped back into the SR and contraction is inhibited. In normal muscles, this increase and decrease in the level of Ca^{++} occurs very rapidly allowing for very precise control of muscle movement.

In dogs with CSS, it is believed that a mutation or mutations in the Ry1 gene result in faulty mechanisms of Ca^{++} control allowing for Ca^{++} leakage. This error of Ca^{++} metabolism makes muscles more susceptible to physiological activators and certain drugs (i.e. caffeine, halothane) that cause Ca^{++} to be released from the SR. Additionally, muscle activation induces excessive Ca^{++} release in the presence of Ry1 mutations. As a result, in dogs with CSS even mild stimuli may cause release of large quantities of Ca^{++} resulting in muscle rigidity. Subsequent rapid depletion of ATP leads to a rapid break down of muscle energy stores resulting in an increased production of muscle lactate.

CSS has been compared to MH in humans, in which affected patients experience muscle rigidity during halothane anesthesia, which induces release of Ca^{++} from the SR. In pigs, Porcine Stress Syndrome (PSS) occurs as a recessive genetic disorder with incomplete dominance since some carriers of the recessive gene (heterozygotes) are stress-prone. Interestingly, this condition occurs with greater frequency in extremely muscular pigs with short, compact body structure and wide hams (large thigh).

Symptoms of CSS. Dogs with CSS appear normal but exhibit intermittent symptoms resulting from the disorder. Episodes associated with CSS may occur spontaneously or after the dog encounters some form of stress such as after periods of exercise, excessive handling, or over-heating. Other stimuli may include eating, fasting, breeding, etc. Muscle tremors proceed to muscle spasms and muscle rigidity, and depending upon the severity of the episode, the dog may completely freeze-up. In less pronounced episodes, the hind limbs will lock-up and collapse and the dog may sway, as if in a drunken stupor, on just the front legs. Open-mouthed breathing (panting) and elevated body temperature are also common. Pupils are dilated and although the dog seems aware of its surroundings, it is unable to respond. Seizures and coma may result depending upon the severity and duration of the episode.

Diagnosis. Identification of CSS susceptible dogs is by testing muscle contraction induced by caffeine, halothane, or ryanodine in biopsied skeletal muscle from the afflicted dog. Because there appears to be a wide variability for expression of the genetic mutation(s) leading to this disorder, some limitations may exist for identifying dogs that experience only mild cases of CSS by this method. Unfortunately, there is currently no genetic test available to identify CSS or genetic carriers of the disorder. Dr. Bruce Smith at the University of Auburn has identified a candidate gene for CSS and is preparing to conduct breeding studies to verify the role of this gene in CSS.

How CSS Causes Seizures. Metabolic encephalopathy (ME) is a disturbance of brain function resulting in neurologic deficits and is caused by disorders of metabolism. Accordingly, ME commonly occurs secondary to CSS because Ca^{++} release channel defects have detrimental effects on the brain and central nervous system.

The brain has limited stores of high-energy phosphates (ATP) and glucose reserves that it requires to maintain neuronal function and cellular integrity. Therefore, the brain is dependent upon glucose and oxygen supplied by blood flow for its energy requirements. Inability to maintain its own energy reserves makes the brain extremely sensitive to metabolic disturbances that deplete energy substrates from the blood.

Loss of calcium homeostasis plays a major role in the development of neurologic dysfunction. Excessive release of Ca⁺⁺ as occurs in some dogs with CSS has effects including but not limited to neurotransmitter release and acute energy depletion. In other dogs with CSS, persistent leakage of Ca⁺⁺ creates a continuous demand for energy. In either of these forms of CSS, the increased demand for energy quickly or persistently depletes the blood of energy substrates required by the brain. One of the major energy requiring functions of the brain is to maintain the resting membrane potential by the sodium/potassium ion pump. When the brain cannot get the energy it requires, the pump fails and the membrane potential decays toward threshold producing the neuron discharge responsible for seizures.

This explains why even mild stimuli such as eating and fasting can result in seizures in the CSS-susceptible dog. Fasting inhibits replacement of blood glucose depleted by elevated energy demands in dogs with leaky Ca⁺⁺ release. Even mildly afflicted dogs that demonstrate low level Ca⁺⁺ leakage will have higher energy requirements. Because eating induces insulin production that will require glucose to balance the insulin levels, additional requirement of glucose during eating will also further compromise a CSS-susceptible dog whose glucose levels are already depleted due to Ca⁺⁺ leakage. This condition of depleted blood glucose levels, which occurs in conjunction with CSS, is known as hypoglycemia and may be one of the principle causes for seizures in CSS dogs.

Treatment. Clinical research exploring the use of calcium channel blockers, such as dantrolene, to treat CSS has resulted in variable efficacy for control of this disorder. Because of the inconsistency for efficacy and because of potential side-effects on cardiac muscles associated with calcium channel blockers in general, more research is required on the use of these drugs in cases of CSS.

Currently, treatment options are directed at treating secondary conditions brought on by the Ca⁺⁺ metabolism defect. Such treatments include use of anti-convulsants to control seizures and glucose therapy to restore depleted sugar in the blood. In dogs that are stressed easily, tranquilizers are often prescribed to reduce CSS episodes during periods that may present high stress to the CSS-susceptible dog (i.e. for use during thunderstorms, vet visits, etc.). Additionally, feeding frequent small meals instead of one or two large meals per day may help the CSS-susceptible dog to maintain adequate blood glucose levels and thus decrease frequency of CSS-related seizures.

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