White Shaker Disease Syndrome

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Introduction and Overview

White Shaker Disease Syndrome is a neurologic disease seen primarily in dogs with white coats, particularly in West Highland White Terriers, Maltese Terriers (Bagley et al., 1993), and Samoyeds (Cummings et al., 1986). Affected dogs have a very unique generalized tremor (unintentional, rhythmic muscle movements) and typically are 5 months to 3 years old when the disease is first recognized (Yamaya et al., 2004). There is no gender predilection for this disease. Because this disease has been identified in breeds of dogs lacking a white coat (Dachshund, among others; Yamaya et al., 2004), and in the adult years of their life, the terms "shaker dog syndrome", "white shaker disease" and "little white shaker dog" commonly are used (Yamaya et al., 2004). The cause of the disease is not known and there is little research being done on this condition in any breed.

Because there are several neurologic and neuromuscular diseases that can produce similar clinical signs, it is essential that Westie owners immediately get a thorough evaluation of their dog and that an accurate diagnosis is made.

Symptoms and Diagnosis

Affected dogs have histories of relatively sudden onset of constant tremors over the body, including the head and eyes (**Figure 7.1**). Opposing muscle groups cause tremors by alternately contracting and relaxing in a repetitive manner (Smith and Thacker, 2004). Uncontrolled eye movements, or opsoclonus, consist of rapid, involuntary, multidirectional (horizontal and vertical) movements of the eyes.

The tremors are exaggerated by excitement, handling, forced locomotion, and high levels of stress (Summers et al., 1995). Although some affected dogs may have constant tremors, they remain alert and responsive to their owners and environment. These dogs generally retain normal sensory and muscle functions, which are controlled by the cranial nerves. Consequently, they are able to sense when their faces are touched, and their pupils dilate and constrict appropriately in response to changes in light. In some instances, tremors may be severe enough to cause a wobbly, uncoordinated gait, or overreaching with the legs when walking forward (Smith and Thacker, 2004). This latter change in gait is called hypermetria.

Because other diseases can manifest as tremors, they must be ruled out before an appropriate treatment can be administered (Smith and Thacker, 2004). Examples of these diseases include various inflammatory or infectious diseases of the nervous system, epilepsy, and exposure to toxic substances such as moldy food, lead or organophosphates. These possibilities are ruled out by performing an electrophysiological evaluation of nerve function and microscopic examination of a portion of a nerve obtained by biopsy. After a variety of diagnostic tests are performed to eliminate the aforementioned possibilities, dogs with typical clinical signs that lack evidence of other diseases are diagnosed with White Shaker Disease Syndrome.

Occasionally, affected dogs may have a head tilt. Because head tilts also can occur other central nervous system disease, peripheral neurologic disorders and even with ear problems, these other causes must first be ruled out before a diagnosis of White Shaker Disease Syndrome is made (Smith and Thacker, 2004).

The diagnosis of White Shaker Disease Syndrome is generally made based on the dog's history, age at onset, and symptoms.

Common Clinical Findings
Terriers at Increased Risk
5 Months - 3 Years Old
Tremors

Blood cytology, chemistry and x-rays, as well as physical examination findings, are usually normal and have not proven valuable to aid in a diagnosis. A sample of cerebrospinal fluid may be collected for analysis, as an increase in the number of lymphocytes has been noted in some cases (Smith and Thacker, 2004). Fortunately, White Shaker Disease Syndrome is rarely a fatal disease.

Krabbe Disease (Globoid Cell Leucodystrophy)

Young Westies also can develop tremors as a result of another neurologic disease that does not appear to be related to White Shaker Disease Syndrome. This disease, which is known as Krabbe disease or globoid cell leucodystrophy (GCL), is a neurologic disease in which a substance that is toxic to the myelin-forming cells in the nervous system accumulates inside nerve cells. Myelin, which makes up most of the white matter in the central nervous system and is present in the peripheral nervous system, is essential for normal nerve function. The accumulation of this substance results in the breakdown of myelin, which leads to severe neurological symptoms such as progressive blindness, seizures, and eventually death.

This disease, which occurs as the result of a deficiency in a specific enzyme called galactocerebrosidase (GALC) that is critical for cellular metabolism, is called a "storage disease." Deficiency of GALC has been demonstrated not only in the brain but also the liver and kidneys of affected dogs (Fletcher et al., 1972; Yunis et al., 1976, Wenger et al., 1999).

> "The tremors are exaggerated by excitement, handling, forced locomotion, and high levels of stress."

West Highland White and Cairn terriers are the two breeds most affected by GCL, which is inherited as an autosomal recessive trait (Parker et al., 1995; Wenger et al., 1999). Clinical signs typically become evident beginning around 3 months of age, and include ataxia of the hindlimbs, muscle wasting, head and body tremors, and even blindness. In many dogs, there are substantial degenerative changes in the peripheral and autonomic nervous systems (Summers et al., 1995), and affected dogs may die from the disease in less than a year or may be euthanized due to poor quality of life (Parker et al., 1995). Pathologists have identified gray discolored areas of the brain in affected dogs, firmness of the cerebral cortex, and dilation of the ventricles, reflecting tissue loss (Summers et al., 1995). The brains of affected dogs appear smaller than normal, with a notable decrease in the amount of white matter (Summers et al., 1995).

To determine if a dog is affected with GCL, a blood sample is analyzed by polymerase chain reaction (PCR) to identify the enzyme deficiency underlying the condition (Cifti et al., 2000). Although not done commonly, examination of a sample of a nerve obtained by biopsy using electron microscopy may aid in reaching a diagnosis and MRI can also be useful (Cozzi et al., 1998; Wenger et al., 1999).

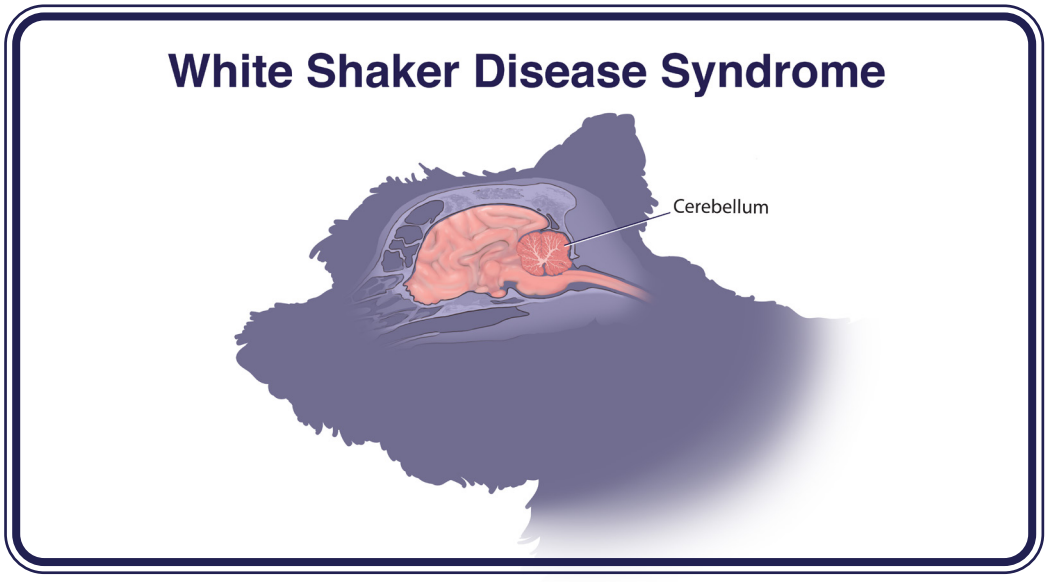

Figure 7.1 - One of the most commonly affected areas of the brain in dogs with White Shaker Disease Syndrome is the cerebellum, which is responsible for 'fine control' of movements.

Krabbe disease has been reported in humans, dogs, mice, monkeys, and sheep (Fletcher et al., 1972). Although death usually occurs before affected infants reach 2 years of age, the disease also has been identified in older people. Canine GCL most closely resembles the late-onset, ultimately fatal form of Krabbe disease occurring in human patients.

Causes

Though the cause remains unknown, White Shaker Disease Syndrome is most often associated with mild inflammation of the central nervous system (non-suppurative encephalomyelitis) (Smith and Thacker, 2004). The cerebellum, which is the part of the central nervous system responsible for 'fine control' of movements, is commonly affected. As a result, dysfunction of this part of the brain could be one of the initiators for the tremor. It is not known if the inflammation is the true underlying cause or if there is an associated neurotransmitter abnormality in affected dogs. Further research should be done to rule out that possibility as well as any virus that might serve as the cause of the disease. There has also been some speculation that White Shaker Disease Syndrome can be congenital in some breeds (West Highland White Terriers, Maltese Terriers, and Samoyeds).

Treatment and Prevention

Early diagnosis of the disease is beneficial in treating affected dogs, as many will respond in a few days to immunosuppressive levels of corticosteroids that have anti-inflammatory effects (Yamaya et al., 2004). The tremors can be reduced with diazepam (Valium), which is used to diminish anxiety or modify behavior, as a muscle relaxant, or an anticonvulsant (Smith and Thacker, 2004). In some cases, dogs will have to remain on a low dose of corticosteroids for the duration of their life in order to remain free of signs of the disorder.

There are a few adverse affects that can occur from taking high doses of corticosteroids. Some of these include vomiting, gastrointestinal bleeding, ulcers, and diarrhea (Smith and Thacker, 2004). Even though these complications can be serious, most can be managed with appropriate care. Unfortunately, there is no known way to prevent the disease.

Some dogs experiencing tremors may have convulsions, and may refuse to eat or seem to be disconnected from their environment just before onset of the seizures. Affected dogs may need to be encouraged to eat and drink. Some owners have noted that hand feeding and raising food and water bowls off the floor is helpful (Swingle C, 2008), and that symptoms can lessen or resolve when the dog is relaxed or sleeping (Summers et al., 1995). Some dogs respond well to being crated in a minimally dark room that is quiet during times of high stress.

In summary, White Shaker Disease Syndrome is a disease that affects primarily white-coated dog breeds, including Westies. Clinical signs, including involuntary tremor, are seen in young dogs. An accurate diagnosis is essential in order to appropriately manage affected dogs, which can be sustained with treatment. Further research is needed to determine the cause(s) of the disease.

Current Research About White Shaker Disease Syndrome

Hammack S, Hague DW, Vieson MD et al. Novel genetic variant associated with globoid cell leukodystrophy in a family of mixed breed dogs. J Vet Intern Med 2023 Sep-Oct;37(5):1710-1715.

Globoid cell leukodystrophy is a fatal autosomal recessive disease caused by variants in the galactosylceramidase (GALC) gene. Two dog breed-specific variants are reported. This study was performed using DNA isolated from a family of dogs with this disease to characterize the putatively causative GALC variant for globoid cell leukodystrophy and from 33 related dogs to determine population allele frequency. A novel GALC variant was identified that likely explains globoid cell leukodystrophy in this cohort. The identification of multiple causal variants for GCL in dogs is consistent with findings in humans.

Corado CR, Pinkstaff J, Jiang X et al. Cerebrospinal fluid and serum glycosphingolipid biomarkers in canine globoid cell leukodystrophy (Krabbe Disease). Mol Cell Neurosci 2020 Jan:102:103451.

Globoid cell leukodystrophy (Krabbe disease) is caused by genetic mutations in the gene encoding, galactosylceramidase (GALC). Deficiency of this enzyme results in central and peripheral nervous system pathology, and is characterized by loss of myelin and an infiltration of globoid cells. The canine model of globoid cell leukodystrophy provides a translational model which faithfully recapitulates much of the human disease pathology. Targeted lipidomic analysis was conducted in serum and cerebrospinal fluid over the lifetime of globoid cell leukodystrophy affected and normal dogs. Psychosine, a substrate of GALC and primary contributor to the pathology in globoid cell leukodystrophy, was significantly elevated in the serum and cerebrospinal fluid by 2 or 4 weeks of age, respectively, and steadily increased over the lifetime of affected animals. Importantly, psychosine concentration strongly correlated with disease severity. This study identified several biomarkers which may be useful in the development of therapeutics for globoid cell leukodystrophy.

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