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Overview of Demyelinating Disorders

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Introduction

Hypomyelination and dysmyelination are disorders of myelin development characterized by axons with thin myelin sheaths or by axons that are nonmyelinated or have abnormal myelin. There are two possible pathologic classifications: 1) thinly myelinated axons with predominantly normal myelin and occasional nonmyelinated axons, or 2) thinly myelinated axons with predominantly abnormal myelin and mainly nonmyelinated axons. These categories have been called hypomyelinating and dysmyelinating disease, respectively, and are characteristic of the congenital myelin disorders seen in young animals. These pathologic changes should not be confused with demyelination, in which there is a breakdown and loss of previously normal myelin. In general, these types of demyelinating diseases do not present clinically as congenital problems.

Etiology and Epidemiology

Demyelinating disorders have been reported worldwide in people, mice, pigs (British saddleback, Landrace), cattle (Hereford, Holstein-Friesian, Jersey, Murray grey, Shorthorn), hamsters, rats, sheep, Siamese kittens and a number of dog breeds, including Chow Chow, Springer Spaniel, Dalmatian, Samoyed, Golden Retriever, Lurcher, Bernese Mountain Dog, Weimaraner, Australian Silky Terrier and mixed breeds. This problem has also been documented in a litter of Vizslas and Catahoula Cur dogs.

In utero infection and heredity are the general causes of hypomyelination. The viruses of classical swine fever, border disease and bovine viral diarrhea have been incriminated but mechanisms responsible for the hypomyelination have not been defined; these three pest viruses are closely related members of the family Togaviridae and are transmitted both vertically and horizontally. The inflammatory neuraxial disorders in domestic animals in which demyelination are canine distemper, visna and caprine arthritis encephalitis syndrome. Most toxins that affect myelin cause demyelination. One in particular, trichlorfon, is an

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organophosphate with a unique toxicity that causes Type A-V porcine congenital tremor syndrome. Pregnant sows treated with trichlorfon during mid and late gestation (days 45–77) produce litters in which up to 90% of the piglets develop a marked tremor syndrome secondary to cerebellar hypoplasia and hypomyelinogenesis.

Other disorders resulting in hypomyelination are hereditary. Almost all of these disorders result in CNS hypomyelination, except in Golden Retrievers, in which hypomyelination of the peripheral nervous system (PNS) has been reported. In CNS hypomyelination, the basic defect involves interference with the functional maturation of oligodendrocytes. The exact mechanisms for the defect are not known but a point mutation on a critical gene has been found in Springer Spaniels. In PNS hypomyelination, the defect involves Schwann cells.

The genetic basis for the inherited hypomyelination syndromes is not fully defined but in most instances, males are affected more often and more severely than females. This supports a sex-linked recessive trait or mode of inheritance.

Clinical Findings

Clinical signs from hypomyelination of the CNS can be seen as early as 10–12 days of age and certainly by the time of weaning. Signs include, most notably, a gross whole body tremor that involves the limbs, trunk, head and eyes. The tremor disappears when the animal is resting or sleeping but reappears on arousal and increases with excitement. The tremors are very noticeable when the animal is eating and are a severe form of intention tremor. In addition, some animals may have difficulty standing and ambulating and may have weakness in the limbs. Secondary to this, postural test reactions may be deficient. Affected animals appear to have vision and other cranial nerve function but occasionally a pendular nystagmus or a jerk nystagmus is seen when the globes are voluntarily moved. These neurologic deficits may be so severe in some animals that euthanasia is warranted. In some breeds of dogs, such as Chow Chows and Catahoulas, the signs usually dissipate over the first year of life and the dogs are normal by 12–18 month of age. In some dogs, the signs may disappear as early as 12–16 week of age.

In Golden Retrievers with PNS hypomyelination, the clinical signs include ataxia, paresis, muscle atrophy and hyporeflexia to areflexia. There is no evidence of CNS hypomyelination in this breed and tremors are not present.

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Lesions

In CNS hypomyelination, gross pathology reveals pallor of the white matter of the brain and spinal cord and possibly a gelatinous appearance. In PNS hypomyelination, the gross changes are minimal and there is no evidence of CNS involvement. In CNS hypomyelination, the microscopic changes include lack of myelin (which is usually severe but not absolute), fewer oligodendrocytes, astrocytes outnumbering oligodendrocytes, oligodendrocytes that differ in appearance from those in healthy animals and abnormal types of glial cells. In PNS hypomyelination, the microscopic changes consist of paucity of myelinated fibers, fibers with inappropriately thin myelin sheaths relative to the caliber of their enclosed axons, occasional fibers with poorly compacted myelin, Schwann cells with larger than normal cytoplasmic volume and increased numbers of Schwann cell nuclei.

Diagnosis

The diagnosis of CNS hypomyelination is made primarily from the spectrum of neurologic deficits and signs and the early age of onset. Unfortunately, histopathology is the only definitive method to confirm a diagnosis. In cases with a heritable basis, pedigree evaluation may be helpful. In cases with a viral cause, confirmation may involve immunofluorescent antibody-staining techniques or virus isolation from nervous tissue (or both). In cases of PNS hypomyelination, biopsy of peripheral nerves is beneficial.

Differential diagnoses include disorders that could cause tremors in young animals. The possibilities are numerous but some of the more common include glycogen storage disease, lysosomal storage disease, cerebellar hypoplasia, encephalitis, hypocalcemia, hypoglycemia, hyperammonemia, toxins (eg, metaldehyde, organophosphates, chlorinated hydrocarbons, fluoroacetate, strychnine, hexachlorophene, bromethalin) and mycotoxins (eg, penitrem-A)

Treatment

There is no specific treatment for hypomyelination. The only means of control and prevention is selective breeding (for heritable syndromes) and immunization (for viral-induced syndromes). If given time to develop normal or further myelin, some animals with congenital hypomyelination syndromes become normal by the age of 12 week to 18 month.