Multisystem Axonopathy and Neuronopathy in Golden Retriever Dogs

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Central axonopathies are uncommon in dogs. Several terms have been used to describe these diseases, such as axonopathy, leukomyelopathy, axonal degeneration, and neuroaxonal degeneration. 1–6 The majority of reported cases were breed-specific with peculiar clinical and pathological features seen in each breed. The association of central axonopathy and motor neuronal degeneration has not been reported. We report a progressive multisystem central axonopathy and motor neuronalopathy in 3 Golden Retriever littermates with unique clinical and pathological features.

Dog 1 was a 3-month-old female intact Golden Retriever dog referred to the Small Animal Clinic of the Ontario Veterinary College (OVC) with a 6-week history of pelvic limb weakness. The owners noticed that the dog appeared smaller than the other littermates and that her pelvic limb musculature was underdeveloped. She had difficulty in getting up, and when resting in lateral recumbency had fine muscle tremors in the limb muscles. The clinical signs progressed to involve the thoracic limbs with generalized weakness observed 2 weeks before presentation.

On physical examination, no other abnormalities were detected except for generalized muscle atrophy. On neurological examination, short-strided tetraparesis, with no evidence of proprioceptive ataxia, was observed. The postural reactions (proprioceptive positioning and hopping) were adequate, as were the cranial nerve reflexes and responses. The flexor and patellar reflexes were mildly decreased. Resting, high-frequency, low-amplitude muscle tremors were seen in all limbs. These tremors could be elicited by palpation of the limb muscles. Based on the findings of lower motor neuron (LMN) tetraparesis, absence of proprioceptive ataxia, normal postural reactions, and mildly decreased reflexes, a neuromuscular disease was suspected.

CBC, biochemical profile, and urinalysis were performed. Abnormalities on the biochemical profile were a creatine kinase (CK) activity of 517 U/L (reference range, 40–255 U/L) and a globulin concentration of 17 g/L (reference range, 21–42 g/L). No cause for the mild hypoglobulinemia was identified and it was assumed to be associated with the young age of the dog. No abnormalities were identified on the CBC or urinalysis. Electromyography, nerve conduction studies, and nerve and muscle biopsies were proposed, but declined by the owners. The dog continued to deteriorate and was re-evaluated at 6 months of age. At that time, the dog was markedly tetraparetic and the patellar reflexes were no longer present. Some extensor muscle tone was still present. Euthanasia and necropsy were performed.

Two other littermates had a similar history and presentation. Dog 2, a male intact Golden Retriever, began to show signs of weakness and tremors at 15 weeks of age. By 5 months of age, severe generalized muscle atrophy and fatigue were obvious. CBC and biochemical profile at that time were normal. The dog was referred and examined at 8 months of age. The neurological examination identified a kyphotic posture (Fig 1), generalized muscle atrophy, neuromuscular type (short-stride) tetraparesis, absence of ataxia, mildly decreased spinal reflexes, and head and body tremors. The nature of the tremors was suggestive of muscle weakness and not intentional tremors as seen with cerebellar disorders. Cranial nerve examination and postural reactions were adequate. CBC and biochemical profile did not identify any clinically relevant abnormalities. Serum and whole blood were submitted for metabolic screening for amino acids, organic acids, and carbohydrates to investigate a possible metabolic or storage disease. Results of these tests were within reference limits. Euthanasia and necropsy were performed.

Dog 3, a male intact Golden Retriever littermate, was presented to the OVC at 8 months of age. Weakness and body tremors were first observed when the dog was 3 months old. At presentation, the dog was marked...
paretic with neuromuscular disease signs, and exhibited a kyphotic posture. The neurological examination findings were similar to those in the other 2 littermates. Physical examination results and general condition seemed worse when compared with the other 2 littermates. The dog was tachypneic, dyspneic, and cyanotic, with a rectal temperature of 40.1°C (104.1°F). CBC, biochemistry profile, and metabolic screening for amino acids, organic acids, and carbohydrates failed to identify any clinically relevant abnormalities. Euthanasia was performed and cerebrospinal fluid (CSF) was collected from the cerebellomedullary cistern immediately after euthanasia. CSF analysis included a white blood cell count of 0 and a protein concentration of 0.18 g/L (reference range, <0.32 g/L).

Complete necropsies were performed on all 3 dogs, and similar pathological findings were seen in all dogs. No gross pathological abnormalities were seen except for severe generalized muscle atrophy.

Brain, spinal cord, nerves, muscles, and representative tissue sections of internal organs were fixed in 10% neutral-buffered formalin, processed, embedded in paraffin, sectioned at 5 μm, stained with hematoxylin and eosin, and examined by light microscopy. Selected sections of the brain and spinal cord were stained with luxol fast blue, cresyl echt violet (CEV), Bielschowsky silver stain, and immunocytochemical stain for neurofilament and glial fibrillary acidic protein.

Multiple serial sections of the spinal cord revealed diffuse axonal degeneration characterized by astrogliosis, axonal swelling, ballooned or absent myelin sheaths, and axons lacking normal myelin sheath (secondary demyelination). Although present in all funiculi, these lesions were more severe in the ventral and lateral funiculi, with the superficial tracts more affected than the deeper tracts (Figs 2–5). Ballooned myelin sheaths contained myelin sheath fragments and axonal debris, also with foamy, plump, finely granular macrophages inside. Some of the macrophages had pyknotic nuclei. In the ventral gray column of the spinal cord, the CEV stain revealed extensive loss of neuronal cell bodies and occasionally a cell body in the process of degeneration at all spinal cord levels. This finding was supported by the results of the Bielschowsky stain (Figs 6, 7).

Histologically, most sections of the brain had no abnormalities, except for the caudal medulla oblongata that had a continuum of the spinal cord astrogliotic lesions. The motor nuclei of the trigeminal nerve also had areas of vacuolation, with some neurons having multiple, large, clear empty cytoplasmic vacuoles.

Multiple nerves were examined, including radial, ulnar, sciatic, and femoral nerves, as well as nerve roots from segments from all regions of the spinal cord. Scattered vacuolation of the myelin surrounding axons within most nerves was seen, with occasional pyknotic macrophages, axonal swelling, and axonal debris. The nerve lesions were more evident in the ventral roots compared with the dorsal roots. The ventral nerve root lesions were thought to represent Wallerian degeneration secondary to cell body loss in the ventral gray column.

Fig 1. Eight-month-old Golden Retriever dog affected with multisystem axonopathy and neuronopathy. Observe the kyphotic posture indicating axial weakness.

Fig 2. Symmetrical lesion in the lateral and ventral funiculi (arrows) and the sparing of the dorsal funiculi (arrowheads). The reactive astrocytes that are replacing the degenerate axons stain brown in the peripheral portions of the lateral and ventral funiculi (arrows). The most severe lesions are the pale brown areas on the surface of the dorsal lateral and ventral funiculi (arrows). Bielschowsky stain. Scale bar = 0.5 mm.

Fig 3. Indentation on the surface of the spinal cord at the dorsolateral sulcus where the dorsal roots enter into the cord. Note the lack of axons and reactive astrogliosis in the dorsolateral funiculus on the left (arrowhead), compared with the normal dorsal funiculus on the right. Bielschowsky stain. Scale bar = 50 μm.
Intercostal muscles and several flexor and extensor muscles from distal and proximal limb portions were evaluated histologically. Pathological findings were suggestive of neurogenic muscle atrophy. In summary, the main pathological lesion in these dogs was diffuse spinal cord leukomyelopathy with concurrent motor neuron degeneration in the ventral horn of the spinal cord.

A number of axonopathies have been described in several canine breeds.2,3,6–9 In general, these diseases share some common features. The lesions are usually bilateral and symmetrical, affecting both the sensory and motor tracts of the spinal cord.1

Because of the involvement of sensory and motor tracts, general proprioceptive ataxia and upper motor neuron paresis are common. The term sensory or hereditary ataxia (eg, hereditary ataxia in the Jack Russell Terrier) is often used to designate some of these cases.3

The dogs of our report are an exception to this rule. None of our dogs exhibited proprioceptive ataxia. Generalized LMN paresis was the primary clinical feature of this disease. This sign primarily reflects the involvement of motor neurons in the ventral gray column of the spinal cord. Despite severe axonopathic changes in the lateral funiculi, where the spinocerebellar tracts are located, general proprioceptive ataxia was not observed. The LMN signs may have prevailed over involvement of the general proprioceptive system.

The distribution of the lesion in this axonopathy and neuronopathy is also unique among the axonopathic diseases reported previously. Labrador Retrievers have a

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**Fig 4.** Luxol fast blue (LFB) stain showing loss of myelin that is pronounced in the tracts in the dorsolateral funiculus of the spinal cord (arrowheads). Astrogliosis has replaced the lost tissue. LFB and cresyl echt violet. Scale bar = 50 µm.

**Fig 5.** Luxol fast blue (LFB) stain showing the loss of myelin that is pronounced in the tracts of the ventral funiculi bilaterally (arrowheads). Astrogliosis has replaced the lost tissue. LFB and cresyl echt violet. Scale bar = 50 µm.

**Fig 6.** Ventral gray column showing depletion of neuronal cell bodies (arrows). Active degeneration of the remaining neurons is shown by their dense staining and the numerous spheroids in the adjacent neuropil (arrowheads). Bielschowsky stain. Scale bar = 100 µm.

**Fig 7.** High power view of the features seen in Figure 6 showing depletion of cell bodies, degeneration of the remaining cell bodies (arrowheads) and spheroids (arrows). Bielschowsky stain. Scale bar = 50 µm.
central axonopathy involving all funiculi of the spinal cord, but the affected dogs were presented with a combination of spinal cord and cerebellar signs and, at necropsy, had aplasia or hypoplasia of the corpus callosum and hippocampal commissure, as well as spina bifida. A hereditary ataxia was reported in young Jack Russell Terriers having a bilateral axonopathy affecting the lateral and ventral funiculi of the cervical spinal cord. However, these dogs were presented with cerebellar signs, and some also had seizures and degeneration of central auditory pathways. Ibizan Hounds also have a diffuse axonopathy affecting all funiculi of the spinal cord, apparently worse in the thoracic area. The gait dysfunction in Ibizan Hounds also resembled a cerebellar disorder and some dogs also had seizures. Muscle atrophy was not seen in these dogs, and despite the absence of the patellar reflex, no changes were seen in the spinal cord gray matter.

Young Scottish Terriers were also reported to have a central axonopathy, characterized clinically by tremors and ataxia. Histologically, these dogs had diffuse degeneration of the spinal cord white matter but also had gliosis and vacuolation of the white matter of the cerebellum, brainstem, and cerebrum; the latter was not present in our cases. Recently, a leukomyelopathy was reported in 2 Leonberger dogs. The affected dogs were young adults and the clinical picture was dominated by ataxia and dysmetria of all limbs. Interestingly, the spinal cord lesions could be seen on magnetic resonance imaging. The lesions were in the dorsolateral funiculi of the cervical spinal cord and were primarily demyelinating, as seen in cases of leukoencephalomyelopathy in Rottweilers.

A multisystem neuronal degeneration has also been reported in young Cocker Spaniels. These dogs had abnormal gait and tremors, but in contrast to our cases had ataxia, obvious signs of thalamo cortical dysfunction, and no spinal cord lesions. A condition reported in Cairn Terriers bears some similarities to the disease reported here. Cairn Terriers have a multisystem chromatolytic neuronopathy that affects motor neurons in the spinal cord ventral horn, brainstem, and thalamic nuclei, which is also associated with Wallerian degeneration in the spinal cord white matter and medulla. The majority of cases had progressive weakness, ataxia, and brainstem signs. In contrast to our cases, none of the reported Cairn Terriers had neuronal loss.

The multisystem axonopathy and neuronopathy reported here also bear similarities to the group of diseases called motor neuron disease (MND) or ventral horn cell disease. Dogs with MND have progressive weakness with muscle atrophy, often accompanied by muscle tremors. Ataxia is not seen because there is no involvement of sensory systems. Spinal reflexes are decreased to absent depending on the disease stage. As the disease progresses, tetraparesis, tetraplegia, cervical ventroflexion, dysphonia, dysphagia, and eventually respiratory failure ensues. Because of the involvement of the intercostal muscles, breathing is impaired and labored, decreasing stamina and the ability to thermoregulate by panting, which can lead to severe hyperthermia. The dyspnea and hyperthermia seen in dog 3 reflect this presentation and likely were caused by the effort the dog made to walk.

MND is well characterized in Brittany Spaniels with 3 phenotypic variants (accelerated, intermediate, and chronic). In the accelerated form, clinical signs were seen between 6 and 8 weeks of age, with severe tetraparesis by 16 weeks of age. In the other 2 forms, clinical signs started when the dogs were between 6 and 12 months of age, with slow progression of signs. The Golden Retrievers of our report had an onset and evolution that differed from the MND seen in Brittany Spaniels, although clinically, the weakness and absence of ataxia were similar. The condition reported here also differs from the other MNDs reported in German Shepherds, English Pointers, and Griffon Biquet Vendee dogs, in which muscle contractures and limb deformities were observed, and with the MND seen in Rottweilers in which the affected dogs had megaesophagus.

Golden Retrievers are predisposed to a few breed-specific neurologic diseases. Myopathic, neuropathic, and neuronopathic diseases have all been reported in this breed. The combination of neuromuscular tetraparesis without ataxia, decreased spinal reflexes, and muscle atrophy in our dogs initially suggested a lesion localized to the neuromuscular system. Muscle dystrophy (MD), which has been well characterized in Golden Retrievers, was an initial differential diagnosis. Golden Retrievers with MD also have neuromuscular tetraparesis, kyphotic posture, muscle atrophy, normal postural reactions, and normal to decreased spinal reflexes. However, the gait of Golden Retrievers with MD has a stiff quality and these dogs exhibit an adduction of the tarsi and a marked decrease in range of jaw motion accompanied by enlargement of the tongue muscles. Only males are affected and they have marked increase in serum CK activity. The dogs of this report had normal or mildly increased serum CK activity and both sexes were affected. The mild increase of CK activity in 1 of the dogs was thought to be related to prolonged recumbency, restraint, or prolonged effort. Recently, a sensory ataxic neuropathy was reported in 16 Golden Retrievers. Although the age of onset of clinical signs was similar to our cases, the disease in our dogs progressed much more rapidly. A main clinical distinction between the multisystem axonopathy and neuronopathy reported here and the sensory ataxic neuropathy is the lack of proprioceptive ataxia or proprioceptive positioning deficits in our dogs. Dogs with multisystem axonopathy and neuronopathy, however, may be presented with severe tetraparesis, and it may be difficult to define the lack of ataxia in these cases. Additionally, if not properly supported, dogs with multisystem axonopathy and neuronopathy may display proprioceptive deficits. Therefore, special attention should be paid to these aspects of the neurological examination. Also, our dogs had severe muscle atrophy, which was not seen in dogs with sensory ataxic neuropathy. There are also several pathological distinctions among these conditions, namely the topography of the spinal cord lesions, with less severe involvement of the dorsal funiculi in our dogs, and motor neuron loss in the ventral horn of the spinal cord.
cord. The findings in the cases reported here differ from those of other neuropathic diseases reported in Golden Retrievers. A young mature Golden Retriever was reported with a sensory neuronopathy. This dog had bilateral axonal degeneration in the dorsal funiculi of the spinal cord (as a reflection of cell body degeneration in the spinal ganglion), but no involvement of other funiculi or ventral gray matter. A hypomyelinating polyneuropathy was also described in Golden Retriever puppies, but the hypomyelination was confined to the peripheral nervous system.

In summary, the clinical and pathological features of this disease have not been observed in other canine neurodegenerative diseases. The main pathologic lesions were diffuse spinal cord axonopathy and motor neuron depletion. Despite severe axonopathic involvement, affected dogs did not have proprioceptive ataxia or proprioceptive positioning deficits, and therefore their clinical presentation resembles that seen with neuromuscular disorders.

Footnote

* Genetic metabolic screening. Section of Medical Genetics. University of Pennsylvania, School of Veterinary Medicine

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References