Peripheral Neuropathy in Twin Calves

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Disorders of the peripheral nerves of domestic animals have been recorded in a number of dog breeds1-4 and in a few cases of ruminants. However, the majority have been of unknown etiology.5,6,9,11

Distal symmetrical polynuropathies have been recognized in genetical, toxic, nutritional, and metabolic disorders in humans4 and other animals.11 The disease is attributed to the dying-back process, the concept of which is that distal regions of nerve fibers are affected primarily in case of the neuronal cyton's trophic function impaired because the axon is dependent on the trophic influence of the nerve cell.13

This article describes morphological findings in twin calves that were affected with sporadically occurring distal symmetrical polynuropathies.

Animals used for this investigation were two male 5-month-old (No. 1) and 6-month-old (No. 2) Holsteins that were twins. A male 5-month-old Holstein without clinical neuromuscular disease was used for the control.

Both cases were euthanized. Tissue blocks collected from the skeletal muscles of the whole body, the central and peripheral nervous systems, and visceral organs were fixed in 10% phosphate-buffered formalin and embedded in paraffin. Sections were stained with hematoxylin and eosin (HE), and reacted for routine (pH 9.4) adenosine triphosphatase (ATPase) and modified (pH 4.3) ATPase.

For histochemical examination, unfixed muscular tissues collected from calf No. 2 (Table 1) were divided into approximately 0.5 cm cubes and immersed in liquid nitrogen (-180°C) for 15 seconds. Serial sections were cut transversely at 10 μm with a cryostat microtome at -20°C, stained with HE, and reacted for routine (pH 9.4) adenosine triphosphatase (ATPase) and modified (pH 4.3) ATPase.

Clinically, calf No. 1 showed abnormal gait with slow walking at 4 months of age. As the condition advanced, calf No. 1 presented progressive muscular weakness of both fore and hind legs, and dysstasia 3 days before necropsy. Calf No. 2 revealed protrusion of fetlock joints in both hind legs at 5 months of age. As the course was steadily progressive, calf No. 2 showed ataxia due to the motor disorder in the legs and inability to stand the day before necropsy (Fig. 1).

According to the owner, these calves were raised by suckling for 3 weeks after birth and given commercial calf-pellets substituted for milk and dried grass during the following days. Other calves reared on the same food were clinically normal. Although their dam was a multiparous cow, these two calves were the first offspring provided with artificial insemination with many dams; however, there was no information on whether other siblings from other dams presented the same symptoms.

At necropsy, the skeletal muscles of both cases were slightly pale. The other organs and tissues were normal. Microscopically, lesions were confined to the peripheral nervous system and skeletal muscles. No abnormalities were seen in any spinal segmental nerve roots, nerve fiber tracts,
or neuronal cell bodies within all levels of the brain, brain stem, and spinal cord.

The most characteristic feature of the nerve fibers was myelinolysis associated with myelin ovoids and regenerating fibers consisting of some small myelinating fibers. Also seen were remyelinating fibers, which were surrounded by
thin myelin sheaths associated with primitive onion-bulb formation (Fig. 2). Longitudinal sections showed vacuolated myelin sheaths containing lamellar debris and macrophages engulfing myelin lipid debris.

In teased nerve fiber preparations, the most conspicuous change was axonal degeneration, characterized by multifocal axonal swelling, segmentation into large ovoids, and clusters of small myelin balls in large diameter fibers (Fig. 3a-d).

The muscular lesions are summarized in Table 1. They were observed symmetrically in both fore and hind legs, and distal leg muscles were affected more severely than the proximal ones. The characteristic changes consisted of solitary or multiple fascicles of atrophic or hypertrophic muscular fibers. In frozen sections, small angular fibers were seen as if they surrounded hypertrophic fibers. The grouping occurred in groups of small-sized fibers as well as in groups of normal-sized and hypertrophic fibers (Fig. 4). The groups of small-sized fibers were mainly composed of type 2 fibers, whereas normal-sized fibers and hypertrophic fibers were of type 1.

The pathological alterations of our cases consisted of axonal degeneration associated with secondary myelinolysis in the peripheral nerve fibers, and severely neurogenic muscular atrophy was observed in distal parts of both fore and hind legs. The brain, brain stem, and spinal cord, including dorsal and ventral nerve roots, were unaffected. In addition, teased nerve fiber preparations demonstrated that large diameter fibers of the peripheral nerves were severely affected. Although it could not be determined at what level of the peripheral nerves these changes began, the distribution pattern of the muscular lesions was indicative of a distal axonopathy attributed to a dying-back process.13,15

The dying-back type neuropathy has been reported in dog breeds as giant axonal neuropathy10,12 and distal symmetrical polyneuropathy. Canine giant axonal neuropathy is an inherited neuropathy characterized by large axonal swelling composed of neurofilaments in the distal portions of certain nerve pathways of the both peripheral and central nervous systems.10,12 A distal symmetrical polyneuropathy in a dog showed pathologically distal muscle atrophy as well as Wallerian degeneration and marked depletion of large diameter myelinated fibers in the distal parts of the appendicular and laryngeal nerves.2 Considerable similarities between the last condition and our cases are present in the distribution pattern of muscular atrophy and lesions restricted to the peripheral nerve fibers in the nervous systems, although morphometrical analysis was not done and the distribution pattern of the peripheral nerve alterations was not definite in our cases. Although primitive onion-bulb formation, suggesting repeated demyelination and remyelination, was observed in our cases, hypertrophic changes, which have been reported in chronic demyelinating neuropathy of dogs, were not apparent.6,7

The pathogenesis of this disease was not determined. However, there was no evidence of diabetic and uremic neuropathies, which have been associated with a distal neuropathy in man14 and other animals.17

On the other hand, a peripheral neuropathy characterized by Wallerian degeneration is reported as a clinicopathological entity in a lactating ewe with “kangaroo gait.”9,8 However, pathological changes appear to be variable, and they relate
to the time from onset of signs. Specifically, spongy changes in the central nervous system, sometimes involving neuronal necrosis, are more prominent shortly after the onset of symptoms, and a peripheral neuropathy appears later, subsequent to neuronal dysfunction and/or degeneration.\textsuperscript{1} The etiology of “kangaroo gait” is thought to be deficiencies of B group vitamins from the action of thiamine and nicotinic acid for the central nervous system.\textsuperscript{1} Although nutritional neuropathy must be considered in our cases, at least our cases differ from “kangaroo gait” by the clinical symptoms, onset of age, and pathological features of the nervous system.

Neurotoxic diseases induced by some industrial and commercial chemicals have been classified according to the primary site of damage as follows: toxic neuronopathy, axonopathy, and myelinopathy.\textsuperscript{9,10} Neurotoxic chemicals producing neuronopathy and axonopathy cause contemporaneous and/or progressive nerve fiber degeneration in the central nervous system as well as in the peripheral nervous system, although the primary affecting site is distinct.\textsuperscript{9} Some chemicals, such as hexachlorophene, tellurium, and lead, are known to induce a demyelinating peripheral neuropathy resulting from myelin edema and splitting of the intraperiod line.\textsuperscript{9} Although there are some pathological similarities between neurotoxic lesions and our cases, it cannot be definitely stated at present whether a certain toxin caused this disease. In addition, other calves reared in the same place and conditions of our cases were normal, and because of this a genetic factor cannot be discounted.

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