Idiopathic Polyneuropathy in Alaskan Malamutes

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Clinical and morphologic features of a progressive polyneuropathy in young mature Alaskan Malamutes are described. Clinical signs included progressive paraparesis, synchronous pelvic limb gait, exercise intolerance, hyperesthesia, hyporeflexia, muscle atrophy, and tetraplegia. Electromyographic testing revealed diffuse fibrillation potentials and positive sharp waves in limb muscles, especially in muscles below the elbow and stifle. Pathologic findings in skeletal muscles and peripheral nerves included neurogenic muscle atrophy, focal or diffuse loss of myelinated nerve fibers, myelinoaxonal necrosis, and variable demyelination or remyelination. Ultrastructural changes included axonal degeneration, presence of numerous Büngner bands, and denervated Schwann cell subunits. The nature and distribution of abnormal electrophysiologic and pathologic findings were suggestive of a distal sensorimotor polyneuropathy, which we have termed idiopathic polyneuropathy of Alaskan Malamutes to distinguish this condition from hereditary polyneuropathy of Norwegian Alaskan Malamutes, last described in 1982.

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Over the past decade, several breed-related peripheral neuropathies have been reported in dogs,[1] including laryngeal paralysis-polyneuropathy complex in young Dalmatian Dogs; laryngeal paralysis in young Bouvier des Flandres and Siberian Husky Dogs[2,3]; congenital hypomyelinating polyneuropathy in Golden Retriever puppies[4]; spinal muscular atrophy in young Rottweilers, Brittany Spaniels, English Pointers, Swedish Laplands, German Shepherd Dogs and Cairn Terriers[5-11]; hypertrophic neuropathy in young Tibetan Terrier Dogs[12]; giant axonal neuropathy in young adult German Shepherd Dogs[13]; distal sensorimotor polyneuropathy in mature Rottweiler Dogs[14]; sensory neuropathies in young Boxer, English Pointer, and Dachshund Dogs[15-17]; globoid leukodystrophy in Cairn and West Highland White Terriers[18]; and fucosidosis in Springer Spaniels.[19] The purpose of the study reported here was to describe clinical and morphologic features of a progressive polyneuropathy in young mature Alaskan Malamutes. This condition has some similarities to an inherited polyneuropathy in Alaskan Malamute Dogs from Norway that was thought to have been eradicated in 1982.[20]

Materials and Methods

Animals

Eleven Alaskan Malamutes (2 males, 9 females; mean [±SD] age, 20 ± 6 months) from 9 litters, with progressive neurologic disease, were evaluated (Table 1). Each dog received clinical and neurologic examinations.[21]

Diagnostic Testing

Diagnostic testing included hematologic and biochemical analyses, ophthalmoscopy, urinalysis, electromyography (EMG) and nerve conduction velocity (NCV) determinations, thyrotropin response testing, blood lead concentration, serum cholinesterase activity, immunologic (eg, antinuclear antibody and lupus erythematosus cell preparation) testing, edrophonium chloride (Tensilon) testing, and spinal radiography. Nerve and muscle specimens were obtained antemortem from 9 dogs (Table 2) and postmortem from dogs 2, 6, and 11. A general necropsy was performed on dogs 6, 10, and 11. Brain, spinal cord, and organ tissues were obtained from these dogs, fixed in neutral buffered 10% formalin, and prepared for paraffin embedding in routine manner. Sections were stained with H & E.

Nerve and Muscle Biopsy Specimens

Muscle and nerve biopsy specimens were mailed by overnight delivery to the Neuromuscular Laboratory, Scott-Ritchey Research Center, Auburn University, for processing in routine manner. Muscle specimens, approximately 1.5 × 1.5 × 1.5 cm, from the biceps femoris, lateral head of the gastrocnemius, flexor carpi ulnaris, cranial tibial, or lateral head of triceps brachii muscle were obtained without use of clamps from dogs under general anesthesia or at necropsy, were placed in glass or plastic bottles, and cooled using gel freeze packs. At the same time, fascicular or full-thickness segments of nerves, common peroneal (at stifle level), distal tibial (at metatarsal level), sciatic (at proximal thigh level), or ulnar (at elbow level), were removed, gently stretched on wooden tongue depressors using pins, and fixed in a mixture of 4% formalin and 1% glutaraldehyde, 2.5% glutaraldehyde in Millonig phosphate buffer (pH 7.3), or neutral 10% buffered formalin. On receipt at the Neuromuscular Laboratory, muscle specimens were oriented in transverse and longitudinal planes, frozen in isopentane precooled in liquid nitrogen, and stored in airtight plastic bottles at −80°C.[22] Serial sections were cut at 8 μm and stained with H & E, modified Gomori trichrome, periodic acid–Schiff, reduced nicotinamide adenine dinucleotide tetrazolium reductase, oil red O, and myosin adenosine triphosphatase (ATPase) at pH 10.2 and 4.3[23] and subtyped.[24] Muscle sections from dogs 6, 7, and 9 were stained with staphylococcal protein A–horseradish peroxidase.[25]

Nerve specimens were cut horizontally into halves and washed in

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Table 1. Signalment Data and Outcome from Alaskan Malamutes with Idiopathic Polyneuropathy

Dog No.	Age (mo) First Signs of Disease/Presentation	Sex	Outcome
1	18/24	F/S	Euthanasia
2	12/18	F/S	Euthanasia
3	19/24	F	Euthanasia
4	12/18	F/S	Euthanasia
5	14/18	F	Euthanasia
6	12/18	M/C	Euthanasia
7	18/20	F	Alive
8	14/18	M	Euthanasia
9	14/18	F	Alive
10	10/12	F	Euthanasia
11	18/20	F	Euthanasia

Abbreviations: F, female; S, spayed; M, male; C, castrated.

phosphate buffer (pH 7.3) at 4°C overnight. One half was further fixed in 1% osmium tetroxide for 6 to 8 hours, placed in 66% glycerin for 24 hours, and stored in 100% glycerin for single teased fiber preparations as described.[26] The second half of each nerve was further fixed in 1% osmium tetroxide for 1 hour, washed in phosphate buffer, transferred through graded ethanol solutions, and processed for embedding in Epon plastic medium. Semithin transverse sections (1 to 2 μm) were stained with paraphenylene diamine.[27] Silver to gray ultrathin sections of nerves were cut, stained with uranyl acetate and lead citrate, and examined by electron microscopy (301 Electron microscope, Philips Instruments Inc, Norcross, GA).

Approximately 100 single fibers per nerve specimen were teased at random from all fascicles, without selection for size or abnormality. They were classified histologically according to Dyck et al[28] (Table 2).

Results

Clinical Findings

The mean age of onset of clinical signs in all affected dogs was 14.6 ± 3.1 months (range 10 to 18 months) (Table 1). Signs of neurologic dysfunction included pelvic limb weakness slowly progressing to thoracic limb weakness, incoordination with stumbling or toe-dragging, synchronous bunny-hopping gait when running, exercise intolerance and collapse, inability to walk up stairs, inability to jump, difficulty standing, muscle atrophy (especially in distal limb muscles), paraspinal (especially lumbar) or appendicular hyperesthesia, hyporeflexia, and proprioceptive deficits. Clinical signs progressed to tetraplegia in dogs 1, 3, 4, 10, and 11. In 1 dog (dog 10), a hoarse bark was first noted at 10 months of age followed by limb weakness 1 month later. Another dog (dog 11) had a mild inspiratory stridor, was tetraplegic, and developed secondary pneumonia. In all dogs, EMG revealed diffuse fibrillation potentials and positive sharp waves in limb muscles. In dogs 1, 3 through 8, and 10, these abnormal spontaneous potentials were recorded mainly in muscles below the elbow and stifle. Motor NCV were either normal or low normal (50 to 60 m/sec in dogs 3, 5, and 11) or slow (28 to 47 m/sec in the ulnar and sciatic/tibial nerves in dogs 6 through 10). In dogs 3, 9, and 10, amplitudes of the proximal (stimulation at coxofemoral joint) and distal (stimulation at hock joint) compound action potentials ranged from 1.1 to 2.4 and 0.9 to 3.0 mV, respectively. These amplitudes were

Table 2. Prevalence (Percentage) of Abnormalities in Teased Nerve Fibers from Alaskan Malamutes with Idiopathic Polyneuropathy

Dog No.	Age (mo) First Signs of Disease/Death	Nerve	Histologic Classification*					Percentage of Abnormal Fibers
			C	D	E	F	G	
1	18/24	Common peroneal	1	0	50	2	2	55 (0)†
2	12/18	Proximal sciatic	0	0	0	0	0	0 (0)
		Common peroneal	0	0	4	12	2	18 (0)
3	19/24	Common peroneal	8	0	20	5	3	36 (0)
4	12/18	Common peroneal	11	1	8	20	1	41 (0)
5	14/18	Ulnar‡	nd	nd	nd	nd	nd	nd (0)
6 (1/7/94)	12/18	Tibial	3	1	45	0	5	54 (0)
(1/27/94)		Sciatic	10	1	13	7	1	32 (0)
		Tibial	1	0	32	2	2	37 (0)
		Saphenous	0	0	7	0	0	7 (0)
7	18/20	Tibial	3	1	18	3	10	35 (0)
8	14/18	Common peroneal	0	0	23	0	8	31 (0)
9	14/18	Common peroneal	7	7	3	18	2	37 (0)
		Ulnar	2	2	2	10	12	28 (0)

Abbreviation: nd, not determined.

* According to Dyck et al,[28] A = normal appearance; B = excessive irregularity of myelin not attributable to preparative artifacts; C = single or multiple regions of nodal lengthening or internodal myelin absence; D = single or multiple C and F abnormalities combined; E = linear rows of myelin ovoids and balls; F = ≥50% difference in myelin thickness between internodes; G = thickening or reduplication of myelin to form globules within internodes.

† Figures in parentheses refer to range of abnormalities reported in comparable nerves from age-matched control dogs.[26,37]

‡ Nerve sample lost for single fiber processing; however, axonal necrosis, demyelination, and nerve fiber loss were observed in semithin tissue sections.

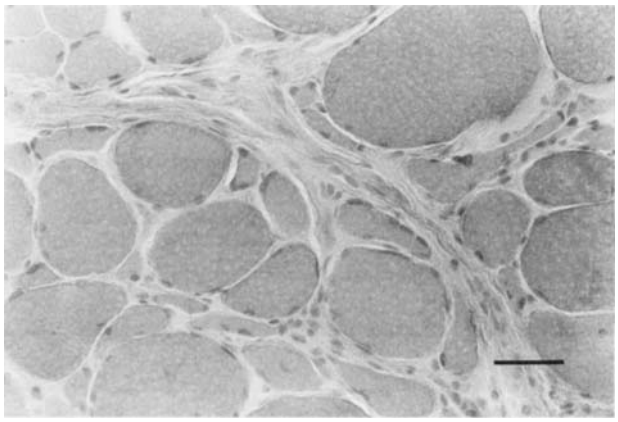

Fig 1. Histopathologic section of skeletal muscle showing marked fiber size variation associated with atrophic and hypertrophic fibers. H & E. Bar = 30 μm.

considered to be decreased. There were insufficient data to determine any difference in motor NCV for proximal versus distal nerve segments in the sciatic/tibial nerve. Sensory NCV of the ulnar nerve was 62 m/sec in 1 dog tested (dog 10). No decremental response to repetitive nerve stimulation was observed in 1 dog tested (dog 8). Results of routine hematologic and blood biochemical analyses and thyrotropin response testing, blood lead concentration, serum cholinesterase activity, and immunologic function were normal. Additional procedures, including ophthalmoscopy, spinal radiography, urinalysis, and edrophonium testing, were negative. Breeding data available from 3 litters indicated that approximately 25% of littermates were affected.

In 7 dogs, management consisted of medical treatment (eg, prednisolone, 1.0 to 2.0 mg/kg PO for 7 to 14 days, followed by a gradually decreasing dosage over 4 to 18 weeks). In 2 dogs, azathioprine (2 mg/kg PO for 5 days, tapered to 1 mg/kg q/48 h) was administered. Most dogs were euthanized because of progressive disease that was unresponsive to therapy. Dogs 7 and 9, however, were 42 months old and 36 months old, respectively, at the time of writing, and neither dog received medication.

Morphologic Findings

Evidence of degeneration or loss of neurons in spinal cord gray matter, brain stem nuclei, or spinal ganglia was not observed in the central nervous system. In dog 11, occasional axonal swelling was observed in the spinal cord, brain stem, and cerebellum. Dorsal and ventral nerve roots appeared normal.

Neurogenic muscle atrophy was observed in most appendicular skeletal muscles and was characterized by fiber size variation associated with atrophic and hypertrophic fibers (Fig 1). Atrophic fibers were angular and sometimes formed small and large groups in a disseminated random distribution. Most of the atrophic fibers were type II, whereas hypertrophic fibers were type I and type II. Fiber type grouping suggestive of reinnervation sometimes was observed. Depletion of myelinated fibers was observed in some intramuscular nerves. Inflammation was not seen in any muscle specimen examined. In dog 4, there was focal myonecrosis and phagocytosis. No antimuscle antibodies were detected using staphylococcal protein A–horseradish peroxidase.[25]

In cross-sectional preparations of nerves from affected dogs, abnormal findings were present in most specimens examined. Changes included focal or diffuse loss of myelinated nerve fibers, myelinoaxonal necrosis, increased endoneurial fibrosis, and occasionally infiltrating macrophages. When multiple samples were procured (dogs 2 and 6), axonal necrosis and nerve fiber loss were more prominent in distal portions of nerves (Fig 2). In some nerve fibers in distal nerves, myelin sheath thickness relative to axonal diameter appeared increased, a finding that suggests axonal atrophy.[28,29] Small groups of regenerating clusters were observed infrequently. In some nerves, demyelination and remyelination were seen, characterized by presence of myelin sheaths inappropriately thin for the caliber of the fiber. Inflammation was not observed in any nerve.

The frequency of abnormalities in teased fibers from different nerves of affected dogs was determined (Table 2). In all dogs, there was a mixture of axonal degeneration and demyelination and remyelination. In nerves of dogs 1, 3, and 6 through 8, axonal necrosis was more prominent, characterized by linear rows of myelin ovoids and balls (grade E; Fig 3). Demyelination (grade C), remyelination (grade F), or both involving the same fiber (grade D) were prominent in nerves of dogs 2, 4, and 9 (Table 2). Proximal and distal nerve specimens (eg, tibial or common peroneal versus proximal sciatic nerve) were obtained in dogs 2 and 6. Abnormalities were found only in the distal nerve sample from dog 2 (Table 2). In dog 6, the frequency of abnormalities (especially axonal degeneration) in the original tibial nerve biopsy was higher than in the sciatic nerve specimen obtained 3 weeks later. The tibial nerve specimen obtained from this dog at the time of the second biopsy had a similar percentage of abnormal fibers as the sciatic nerve, but the frequency of axonal degeneration was higher in the distal specimen (Table 2). The only sensory nerve examined was the saphenous nerve from dog 6, and axonal degenerative changes were observed in approximately 7% of teased fibers.

Ultrastructurally, peripheral nerves from affected dogs were characterized by loss of myelinated fibers, marked increase in endoneurial collagen, axonal degeneration (Fig 4), multifocal myelinoaxonal necrosis (Fig 5), numerous Büngner bands (conglomerations of Schwann cells previously associated with myelinated axons)[29] (Fig 6), multifocal macrophage infiltration, occasional regenerating clusters, and presence of dark endoneurial fibroblasts. Macrophages occasionally were seen within the Schwann cell cytoplasm of myelinated fibers containing degenerating axons. Another axonal alteration included watery appearance of axons with apparent loss of normal cytoskeletal components but surrounded by an intact myelin sheath. Myelin debris, membranous bodies, and prominent organelles, especially mitochondria, sometimes were observed in axons and Schwann cell cytoplasm. There was no evidence of axonal neurofilamentous accumulations or tubulovesicular aggregates. In unmyelinated fibers, there were multifocal collagen pockets, flat

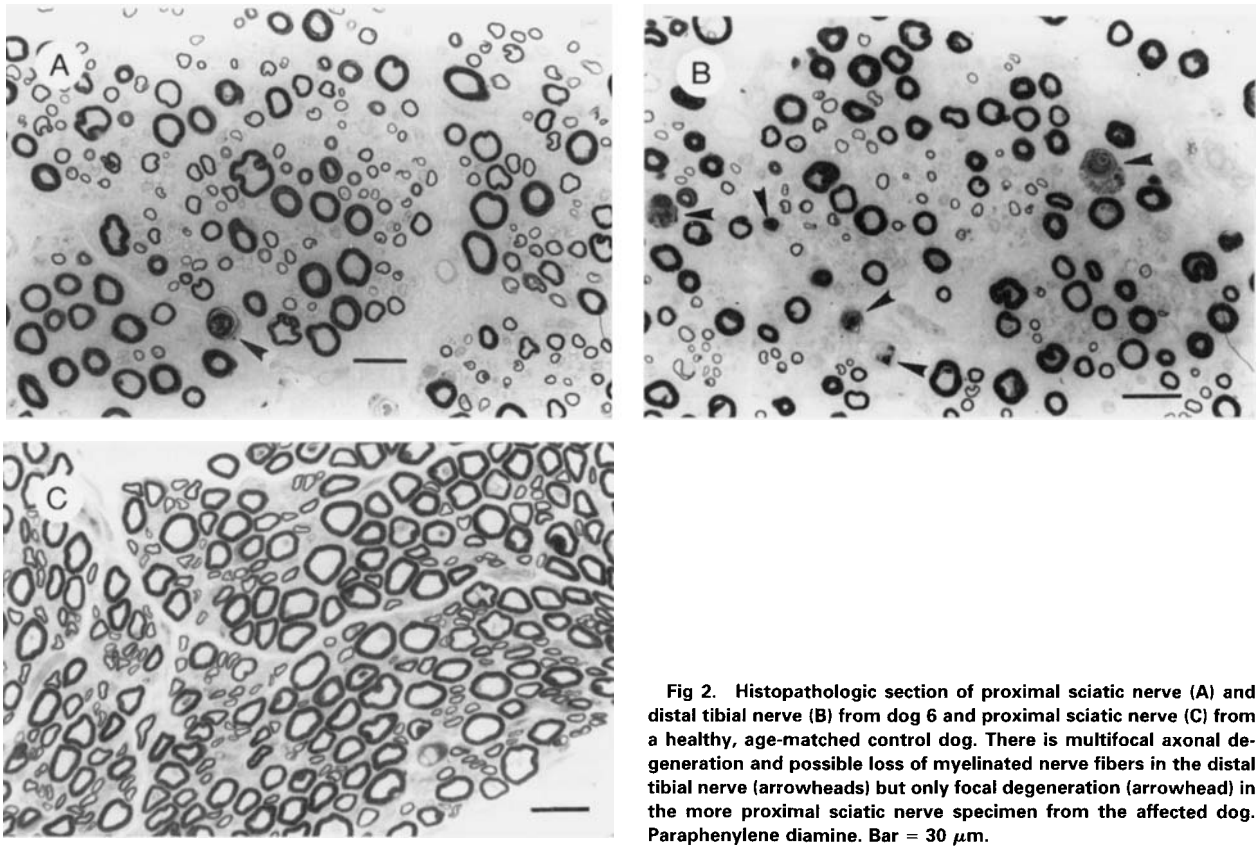

Fig 2. Histopathologic section of proximal sciatic nerve (A) and distal tibial nerve (B) from dog 6 and proximal sciatic nerve (C) from a healthy, age-matched control dog. There is multifocal axonal degeneration and possible loss of myelinated nerve fibers in the distal tibial nerve (arrowheads) but only focal degeneration (arrowhead) in the more proximal sciatic nerve specimen from the affected dog. Paraphenylene diamine. Bar = 30 μm.

axons, empty or denervated Schwann cell subunits (Fig 7), intra-axonal membranous accumulations, and swollen, watery axons. Vessels appeared normal. Demyelinating fibers were seen only rarely, although in some nerves, there was focal presence of thinly myelinated fibers, suggestive of remyelination. There was no evidence of onion bulb formation.

Discussion

The signalment, history, clinical signs, and pathologic findings suggest a sensorimotor polyneuropathy in Alaskan Malamutes. The pathologic changes in affected Alaskan Malamutes were characterized by variable neurogenic muscle atrophy secondary to a peripheral neuropathy that was dominated by axonal degeneration. Changes were found both in motor and in sensory nerves. Cross-sectional and ultrastructural studies of nerve specimens point to an underlying

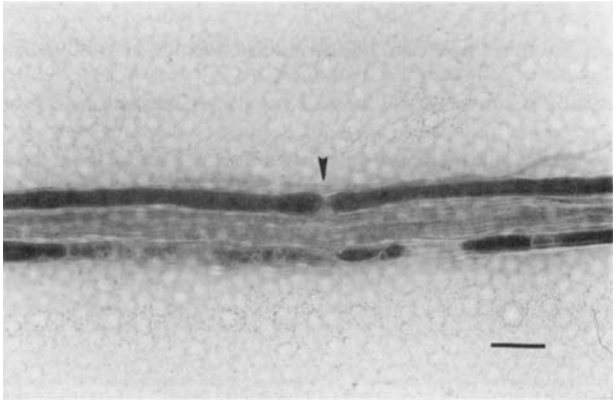

Fig 3. Histopathologic section of two teased nerve fibers. Top specimen is a normal myelinated fiber with node of Ranvier (arrowhead). Bottom specimen depicts a degenerating fiber with linear rows of myelin ovoids and balls. Osmium tetroxide. Bar = 25 μm.

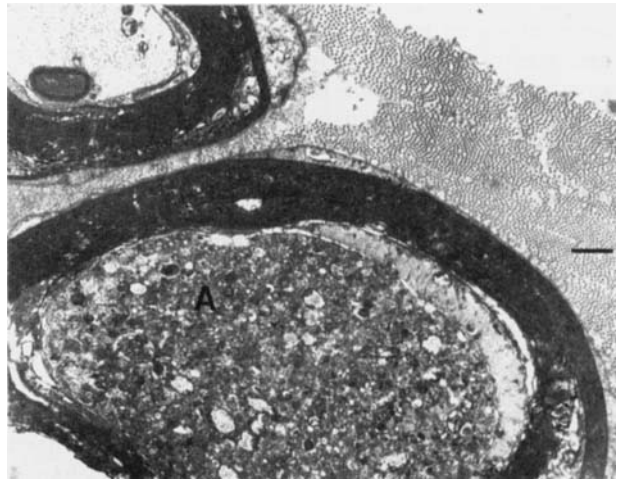

Fig 4. Electron micrograph of a section of common peroneal nerve showing axonal degeneration in a large-caliber myelinated fiber (A). Part of the axon, with normal-appearing neurofilaments, appears as a marginated crescent under the myelin sheath from approximately 12 to 3 o'clock (B). Uranyl acetate. Bar = 1 μm.

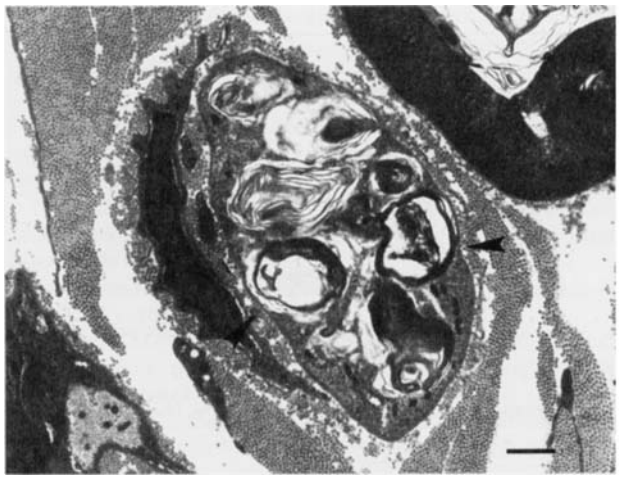

Fig 5. Electron micrograph of a section of common peroneal nerve showing a fiber undergoing myelinoaxonal necrosis (arrowheads). Uranyl acetate. Bar = 1 μm.

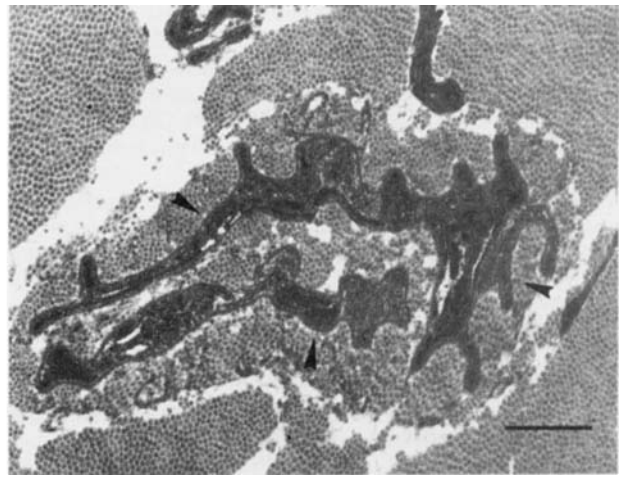

Fig 7. Electron micrograph of a section of distal tibial nerve showing several flattened Schwann cell profiles (arrowheads) and loss of axons in unmyelinated fibers. Uranyl acetate. Bar = 1 μm.

primary axonopathy, based on apparent loss of myelinated nerve fibers, presence of numerous bands of Büngner or denervated Schwann cells, and scattered myelinoaxonal necrosis characterized by ovoids containing a mixture of disintegrating myelin segments and degenerated axonal components.[28-30] Membranous material with myelin-like appearance seen in affected axons suggests early axonal degeneration.[14] Further evidence for a primary axonopathy in affected dogs is the involvement of unmyelinated nerve fibers, as suggested by the presence of collagen pockets, increased numbers of profiles in Schwann cell subunits, and increased numbers of subunits devoid of axons.[29-32] In single nerve fiber preparations, axonal degeneration was the most dominant abnormality in 8 of 12 nerves examined. The high frequency of demyelination and remyelination in teased nerves of some affected dogs was considered to be secondary to axonal degeneration.[28] The mechanism of paranodal and segmental demyelination in axonal degeneration is poorly understood but may result from alterations in volume of the axonal cylinder (eg, axonal atrophy and swelling).[28,29] Demyelination and chronic axonal changes have been reported in several neuropathies of dogs, including distal sensorimotor polyneuropathies of mature Rottweilers[14] and other large-breed dogs,[33] distal sensory neuropathy in long-haired Dachshunds,[16] and chronic laryngeal paralysis-polyneuropathy complex in young Dalmatians.[1] Evidence of chronic demyelination and remyelination with onion bulb formation, as reported in nerves of horses with distal axonopathy associated with idiopathic laryngeal hemiplegia,[34-36] was not seen in the Alaskan Malamutes.

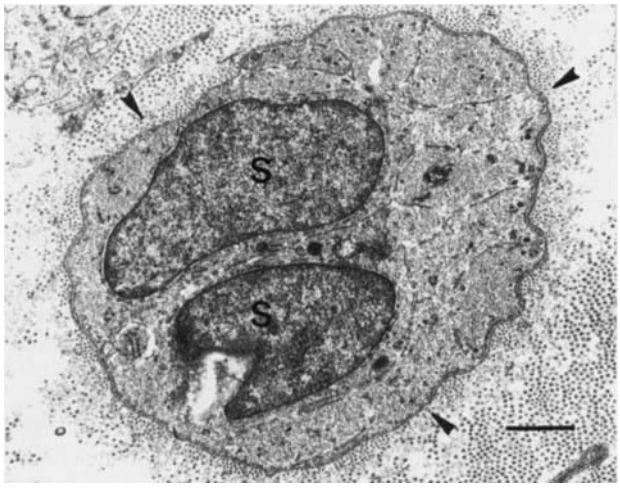

Fig 6. Electron micrograph of a section of distal tibial nerve with Büngner band (arrowheads) containing two Schwann cell nuclei (S). Uranyl acetate. Bar = 1 μm.

The nature and distribution of abnormal electrophysiologic findings in muscles below the elbow or knee in 8 of 11 dogs were suggestive of a distal polyneuropathy.[1,14,33] These data were supported by more severe loss or degeneration of myelinated nerve fibers in semithin cross-sectional nerve preparations of distal nerves from 2 dogs in which proximal and distal nerve segments were examined. Prospective quantitative and qualitative studies on proximal and distal nerve specimens from other affected Alaskan Malamute Dogs are necessary to confirm or exclude the presence of distal nerve disease. Distal neuropathies have been reported in Rottweilers[14] and giant-breed dogs,[34] in German Shepherd Dogs with hereditary giant axonal neuropathy,[13] in dogs with diabetic neuropathy,[37] in long-haired Dachshunds with hereditary sensory neuropathy,[16] and in Dalmatians with laryngeal paralysis-polyneuropathy complex.[1] A number of pathogenetic mechanisms have been offered to explain these distal or dying back neuropathies: primary toxicity of the nerve cell body,[38] Schwann cell abnormalities,[39] primary axonal changes,[40] and disrupted axonal flow.[41]

The cause of polyneuropathy in these Alaskan Malamutes is undetermined. No dog in our study had evidence of meta-

Table 3. Comparison of Hereditary (HPAM) and Idiopathic (IPAM) Polyneuropathy of Alaskan Malamutes

	HPAM	IPAM
Course	Chronic	Chronic
Age of onset	12–18 mo	10–18 mo
Weakness, tetraplegia, exercise intolerance	Yes	Yes
Coughing, dyspnea, regurgitation	Yes	Not seen to date
Proprioception, pedal reflex	Normal	Abnormal
Patellar reflexes	Decreased or absent	Decreased or absent
Megaesophagus	Yes	No
Hyperesthesia	Occasionally in paws	Frequent, paraspinal or appendicular
Electrodiagnostics/ electromyography	Proximal/distal abnormalities	Usually distal abnormalities
Pathology	Variable neurogenic atrophy, fiber type grouping	Variable neurogenic atrophy, fiber type grouping
Appendicular muscles		
Laryngeal muscles	Atrophy	Not examined
Nerve	Degenerative changes at all levels; primarily demyelination	Primarily distal axonal degeneration
Spinal cord	Minimal to mild fiber degeneration in white matter	Normal to minimal white matter changes
Treatment	Unresponsive	Unresponsive
Prognosis	Guarded to favorable, recurrences likely	Guarded
Mode of inheritance	Autosomal recessive	Unknown, possibly autosomal recessive
Breeding control and restrictions	Effective control. Last known case in 1982	Unknown

bolic, toxic, or autoimmune disease. The occurrence of this condition in Alaskan Malamutes strongly suggests a genetic disease. Although pedigree data are incomplete, an autosomal recessive mode of inheritance is suggested because the disorder occurred in approximately 25% of littermates from 3 different breedings (dogs 1, 8, and 10). The age of onset (10 to 18 months) is unusually late for inherited neuropathies in dogs.[42] Delayed onset, however, occurs in German Shepherd dogs with inherited giant axonal neuropathy.[13]

Idiopathic polyneuropathy in Alaskan Malamutes (IPAM) is similar to hereditary polyneuropathy in Norwegian Alaskan Malamutes (HPAM), last reported in 1982.[20] Features of these 2 peripheral nerve diseases are summarized in Table 3. Signalment, age of onset, and clinical course are similar in both conditions. With HPAM, clinical improvement usually was observed after several weeks without treatment.[43] Some dogs have lived several years after regaining ability to walk. Recurrence of paraplegia or tetraplegia was observed commonly.[43] In our dogs with IPAM, 9 of 11 were euthanized because of unremitting tetraparesis or tetraplegia. The remaining 2 affected dogs, which were 42 months old (dog 7) and 36 months old (dog 9) at the time of writing, were less severely affected clinically than the others. One of these dogs (dog 7) continued to manifest a bunny-hopping gait, mild weakness, and variable lumbar hyperesthesia for at least 2 years after onset of signs. The second dog (dog 9), a littermate to a severely affected dog (dog 8) that was euthanized, clinically was the least severely affected dog in our series. Coughing, regurgitation, and megaesophagus were frequently observed in dogs with HPAM[20,43] but were not seen in our dogs except dog 11, which had mild inspiratory stridor and secondary aspiration pneumonia. Electromyographic abnormalities were similar in both conditions, but the distribution of these abnormalities was different. Electromyographic abnormalities involved proximal and distal limb musculature in HPAM but predominantly distal muscles in IPAM. Slowed NCV occurred in both diseases. Pathologic similarities were noted in skeletal muscles, but prominent neurogenic atrophy was observed in the laryngeal muscles of several dogs with HPAM.[20,43] Presumably this finding reflected laryngeal paralysis and accounted for coughing and exercise intolerance in these dogs. Laryngeal muscles have not been examined in dogs with IPAM because of the lack of clinical signs suggestive of laryngeal paralysis. The peripheral nerve fiber degeneration reported in HPAM was observed at all levels, including spinal roots.[20,43] In our dogs, preliminary pathologic studies indicate a preferential distal degeneration of nerve fibers. Motor and sensory nerves are affected in both conditions. Ultrastructural studies of peripheral nerve suggested that demyelination was the primary lesion in HPAM (L Moe, personal communication). In contrast, axonal degeneration appears to be the dominant underlying lesion in dogs with IPAM. In both conditions, only mild changes occur in the central nervous system and include focal or scattered axonal and myelin sheath swellings in the white matter of spinal cord or brain stem.

It seems unlikely that two different neuropathies having similar age of onset and clinical course would occur in the same breed of dog. Nevertheless, important distinctions exist clinically, pathologically, and prognostically to warrant a separate classification at this time. We propose that the term idiopathic polyneuropathy of Alaskan Malamutes be used to distinguish this condition from HPAM until additional stud-

ies are available. Pedigree analysis is required to confirm the suspected autosomal recessive hereditary nature of IPAM.

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