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Tongue atrophy as a neurological finding in hereditary polyneuropathy in Alaskan malamutes

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Abstract

Background: Tongue atrophy with wrinkling as a clinical sign of inherited polyneuropathies has not been reported in dogs.

Objectives: Clinically describe tongue atrophy as well as morphology of the tongue and hypoglossal nerve in Alaskan malamute polyneuropathy (AMPN).

Animals: Six client-owned Alaskan malamute dogs diagnosed with AMPN, all homozygous for the causative mutation in the *N-myc downstream-regulated gene 1* (*NDRG1*) and 1 neurologically normal control Alaskan malamute.

Methods: Prospective case study. Clinical and neurological examinations were performed on affected dogs. Necropsy samples from the tongue muscle and hypoglossal nerve were examined by light and electron microscopy.

Results: All affected dogs had abnormal wrinkles and grooves on the dorsal surface of the tongue, a clinical sign not described previously in dogs with AMPN. Electromyography of the tongue performed in 2 dogs showed spontaneous activity. Five affected dogs underwent necropsy studies. Histopathology of the tongue showed groups of angular atrophic myofibers and changes in the hypoglossal nerve included thinly myelinated fibers, small onion bulbs, folded myelin, and axonal degeneration.

Conclusion and Clinical Importance: Histopathologic changes in the tongue and hypoglossal nerve were consistent with previously reported changes in skeletal muscle and other nerves from dogs with AMPN. Therefore, we conclude that macroscopic tongue atrophy is part of the disease phenotype of AMPN and should be considered a potential clinical sign in dogs with polyneuropathies.

KEYWORDS
Alaskan malamute polyneuropathy, Charcot-Marie-Tooth type 4D, hypoglossal nerve, *NDRG1* mutation

Abbreviations: AChR ab, acetylcholine receptor antibody; AMPN, Alaskan malamute polyneuropathy; CMT4D, Charcot-Marie-Tooth disease type 4D; EMG, electromyography; fT4, free thyroxine; HMSNL, hereditary motor and sensory neuropathy—Lom; MG, myasthenia gravis; MNCV, motor nerve conduction velocity; MuSK-abs, muscle-specific tyrosine kinase antibodies; NDRG1, N-myc downstream-regulated gene 1; TSH, thyroid stimulating hormone; TT4, total thyroxine.

1 | INTRODUCTION

Hereditary polyneuropathy in the Alaskan malamute dog breed was first described in Norway in the 1980s[1-3] and additional phenotype

characteristics were later described.[4,5] Affected dogs typically displayed slowly progressive clinical signs with onset at 3 to 19 months of age, characterized by exercise intolerance, pelvic limb ataxia, inspiratory stridor, tetra paresis and muscle atrophy. Electromyographic (EMG) evaluation showed spontaneous activity in several skeletal muscles of the thoracic and pelvic limbs and decreased motor nerve conduction velocity (MNCV). Histopathology identified a degenerative polyneuropathy of both sensory and mixed nerves.[2-4] In 2013, a missense mutation (p.Gly98Val) in the *N-myc downstream-regulated gene 1* (*NDRG1*) was identified as the cause of peripheral polyneuropathy in the Alaskan malamute.[4] In humans, a mutation in *NDRG1* leads to Charcot-Marie-Tooth disease type 4D (CMT4D), also known as hereditary motor and sensory neuropathy-Lom (HMSNL).[6-8] Type 4D disease is a subtype of Charcot-Marie-Tooth disease, the most common group of hereditary polyneuropathies in people.[9] Clinical signs reported in humans include lower limb weakness, muscle wasting, and deafness.[7,10] In 1 study, tongue atrophy was reported in 26% of 35 affected humans, but no further details were provided.[10] The tongue muscle is innervated by the hypoglossal nerve, which originates in the brainstem. A lesion in this nerve might cause alterations to the tongue muscle seen as neurogenic atrophy.[11] Both CMT4D[6,8] and Alaskan malamute polyneuropathy (AMPN)[5] are considered primary demyelinating neuropathies, and histopathological changes include demyelination, remyelination, small onion bulbs and secondary axonal loss.

We first observed abnormal tongue appearance in an affected Alaskan malamute in 2013. Tongue appearance may be a previously overlooked but important clinical finding in the investigation for polyneuropathies in dogs. In addition, the appearance of the tongue might be recognized as atypical by owners and veterinary clinicians. Thus, examination of the tongue could be helpful in AMPN diagnosis. To determine whether it is a consistent clinical finding in dogs with polyneuropathy, a systematic analysis of tongue appearance and histopathology was carried out in Alaskan malamutes with neurological signs typical of AMPN.

No reports of dogs with inherited polyneuropathies have been published that describe macroscopic and histopathological changes in the tongue. Our aim was to report the recently identified clinical sign of abnormal tongue appearance in dogs with AMPN, as well as a morphological description of pathological changes in the tongue musculature and hypoglossal nerve.

2 | MATERIALS AND METHODS

2.1 | Animals and ethics

This prospective case series was designed as a sequential case study between August 2013 and November 2020 at the Norwegian University of Life Sciences, Faculty of Veterinary Medicine. Dogs included were client-owned Alaskan malamutes genotyped using the previously described Taqman assay.[4] Dogs included as affected had neurological signs typical for AMPN, such as exercise intolerance, ataxia, inspiratory stridor and hyporeflexia,[2,3] and were homozygous for the p.Gly98Val mutation in *NDRG1*. One neurologically normal Alaskan malamute homozygous for the wild type *NDRG1* allele was included as a control dog. The control dog was euthanized at the owners request for unrelated, nonneurological reasons. Written consent for euthanasia, necropsy and tissue sampling were obtained from all dog owners. Euthanasia was performed using IV pentobarbital injection. Ethics approval was not required for this study because all sampling was undertaken as part of standard diagnostic procedures or necropsy. Analysis of other tissues from the same dogs included in the present study have been presented elsewhere.[5,12]

2.2 | Clinical and diagnostic evaluation

Medical records of the included dogs were reviewed and analyzed. Neurological and general physical examinations were performed in all affected dogs and a neurological examination was performed in the control dog. Results of diagnostic tests such as CBC, serum biochemistry, bile acid concentrations, serum electrolyte concentrations, thyroid testing (free thyroxine [fT4], total thyroxine [TT4], thyroid stimulating hormone [TSH]), acetylcholine receptor antibodies (AChR ab), routine urinalysis and electrodiagnostic evaluations (EMG [electroymyography] and MNCV [motor nerve conduction velocity]) were reviewed when available. Electrodiagnostic examinations were performed using a Synergy N2 machine.

2.3 | Sampling for light and electron microscopy

Samples from the tongue and hypoglossal nerve were taken as part of routine necropsy examination, as previously described.[5,13] Briefly, samples from the tongue were fixed in 10% buffered formalin, paraffin-embedded and stained with hematoxylin and eosin. Images were taken using an Axio Imager 2 microscope equipped with an Axiocam 506 color camera. Samples from the intracranial portion of the hypoglossal nerve were fixed in 2.5% glutaraldehyde in Sorensen's phosphate buffer (0.1 M, pH 7.4), postfixed in 1% osmium tetroxide and embedded in epoxy. Semithin sections (0.5 μm) were stained with toluidine blue and safranine-O. Ultrathin sections (70 nm) were contrasted with uranyl acetate and lead citrate, and examined using a FEI Morgagni 268 transmission electron microscope equipped with an Olympus Veleta CCD camera. Morphometry including the *g* ratio (axonal diameter divided by total nerve fiber diameter) was performed as previously described.[5]

3 | RESULTS

3.1 | Animals

Seven Alaskan malamute dogs were included in the study. Six of these were affected dogs from 4 different litters (5 intact females and

1 intact male) and 1 was an unaffected control dog (intact female). Three of the affected dogs were littermates. Median age at onset of clinical signs was 11.5 months (range, 7-24 months). Three of 6 dogs were euthanized at the owners' request shortly after first presentation to the Faculty of Veterinary Medicine, Small Animal Teaching Hospital because of severe clinical signs and homozygosity for the *NDRG1* mutation. Median follow-up time for the 3 remaining dogs with AMPN was 5 years (range, 1 month-6 years). Six of the dogs (5 affected and 1 control dog) were euthanized at the owners' request and histopathology of the tongue muscle and hypoglossal nerve was assessed. One affected dog was euthanized several years later in another part of the country because of severe dyspnea, and histopathology of the tongue and hypoglossal nerve therefore was not performed. The median age at euthanasia of the affected dogs (n = 5) was 7 years (range, 3-9 years). The control dog was euthanized at 8 years of age. An overview of the affected cases is presented in Table S1.

3.2 | Clinical presentation

Dog owners reported clinical signs of dysphonia, inspiratory stridor, general weakness, exercise intolerance, collapse, and tremors of the pelvic limbs in the affected dogs. Onset of clinical signs is presented in Table S1. Clinical and neurologic evaluation identified changes in tongue appearance, consisting of wrinkles (n = 6), grooves (n = 1), and fasciculations (n = 2), which were symmetrically distributed when comparing the right and left side of the tongue (Figure 1). There was no history of other factors that could be associated with the observed tongue appearance. None of the dog owners had noticed the abnormal tongue appearance before veterinarians brought it to their attention. In 1 of the affected dogs, observable tongue atrophy was seen at repeated examinations at 7, 8, and 9 years of age. Difficulties associated with food prehension were not reported. Other abnormalities identified at clinical examination were general muscle atrophy, ataxia, noisy breathing associated with laryngeal paresis, proprioceptive deficits and hyporeflexia.

FIGURE 1 Macroscopic tongue appearance from an (A) affected and (B) unaffected Alaskan malamute dog. In the affected dog (A) the tongue had apparent striations and folds on the dorsal surface which was not observed in the tongue of the unaffected dog (B)

3.3 | Clinical pathology

Results of hematology (6/6), serum biochemistry (6/6), bile acids (6/6), serum electrolyte concentrations (6/6), serum fT4, TT4 and TSH concentrations (6/6), AChR ab (4/6) and urinalysis (3/6) did not disclose any specific abnormalities in the affected Alaskan malamutes. The control dog had a markedly increased C-reactive protein concentration of 164 mg/L (reference interval, 0-15 mg/L), marked neutrophilia, monocytosis and mild nonresponsive anemia, and was diagnosed with neoplasia in the myocardium.

3.4 | Electrophysiology

Routine electrodiagnostic examination was performed in 4 of the affected Alaskan malamutes and showed spontaneous activity in several skeletal muscles and abnormally slow MNCV in the ulnar and peroneal nerves (Table S1). In 2 of the dogs, EMG of the tongue was performed and showed moderate spontaneous activity as evidenced by fibrillation potentials and positive sharp waves.

3.5 | MORPHOLOGICAL FINDINGS

Increased variation in muscle fiber diameter was present in the tongue of all affected necropsied dogs (n = 5; Figure 2A-D). Multifocal atrophic and hypertrophic muscle fibers were observed in the samples. The atrophic fibers were present as scattered angular myofibers or small groups of fibers with circular outline. Some of the hypertrophic fibers had several internal nuclei. Additionally, in samples from 2 of the affected dogs, degeneration and necrosis of myofibers were present. The affected fibers were fragmented, lacked the characteristic striated pattern of normal muscle fibers and had homogenous eosinophilic sarcoplasm.

In teased nerve fibers (n = 2), myelin thickness varied between internodes along the same nerve fiber (Figure 3A). In semithin sections of the hypoglossal nerve (n = 4) many of the axons were inappropriately thinly myelinated for the axon diameter (Figure 3C), and some were surrounded by concentrically arranged cells (suggestive of small onion bulbs), both findings indicative of previous episodes of demyelination and remyelination. Ultrastructural analysis (n = 4) confirmed the presence of onion bulbs (Figure 4A). Additionally, thinly myelinated fibers with basophilic material adaxonally were observed in semithin sections (Figure 3C). This change was further examined by transmission electron microscopy, and consisted of folded myelin in the inner part of the myelin sheath (Figure 4B), pleomorphic material in the adaxonal Schwann cell cytoplasm (Figure 4C) or both. The

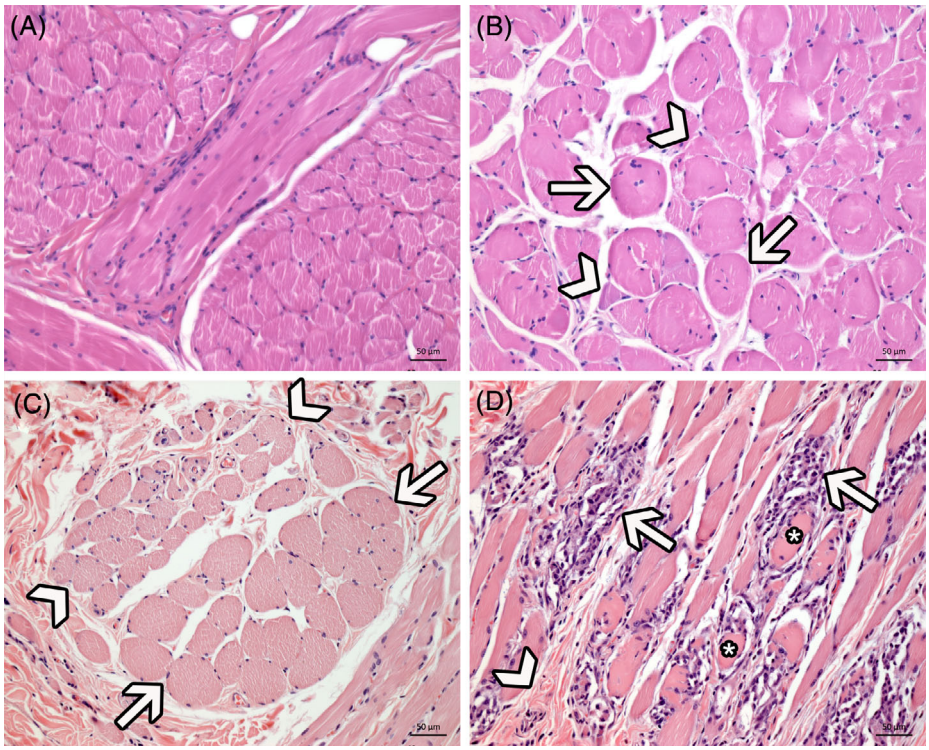

FIGURE 2 Light micrographs of muscle (A-D) from affected (B-D) and control (A) Alaskan malamutes. No changes were observed in the tongue muscle (A) of the control dog. In the tongue muscle of affected Alaskan malamutes, an increased variation in myofiber diameter was present. Atrophic fibers were present as scattered, angular myofibers (B, arrow heads) and groups of small fibers (C, arrow heads). Additionally, hypertrophic fibers were present (B, C, arrow), occasionally with internal nuclei (B, arrow). In two of the affected dogs, segmental necrosis of myofibers were present. The necrotic fibers were fragmented with homogenous eosinophilic cytoplasm (D, asterisks), and surrounded by an increased number of mononuclear cells (D, arrows) and fibrosis (D, arrow head)

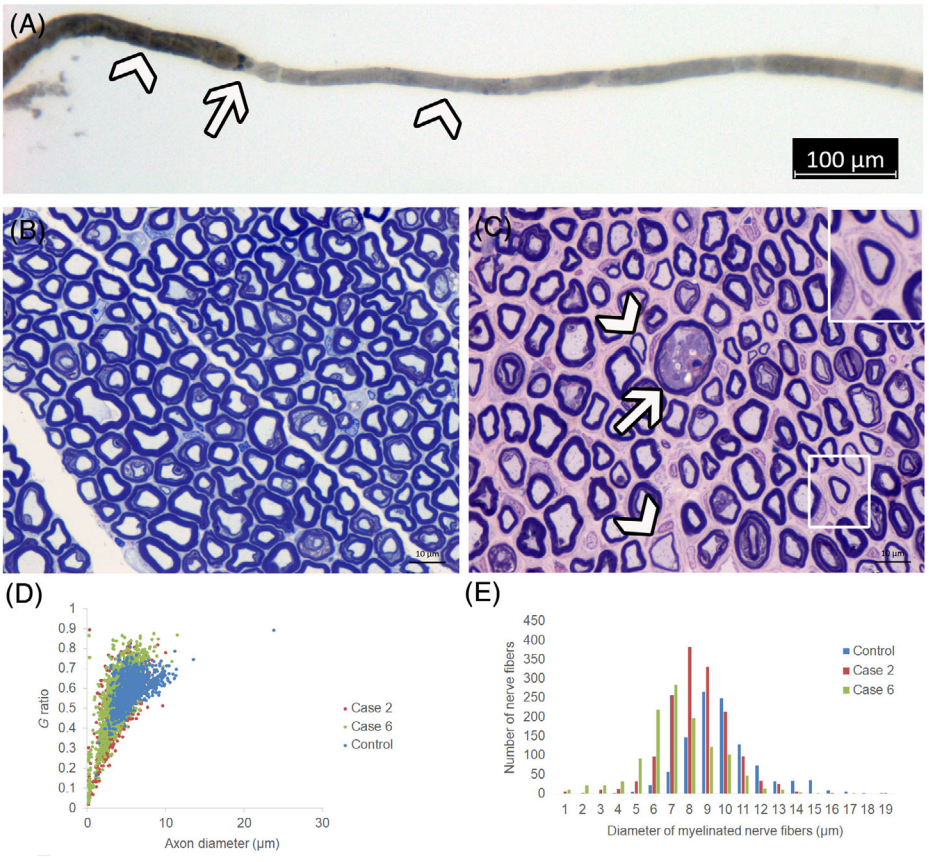

FIGURE 3 Light micrographs of hypoglossal nerve from affected (A, C, D) and control (B) Alaskan malamutes. In teased fibers (A), the myelin thickness varied between internodes (arrow heads) along the same nerve fiber. A node of Ranvier is indicated with arrow. In the hypoglossal nerve, thinly myelinated (remyelinated) fibers were present (C, arrow heads). Degenerative nerve fibers (C, arrow) and presumptive onion bulbs (C, white frame and inset) were further examined in the electron microscope. *G* ratio/axon scatter plot (D) demonstrates a proportion of middle-sized axons with increased *g* ratios and small axons with decreased *g* ratios in the hypoglossal nerves of affected dogs. Furthermore, the myelinated fiber diameter distribution is shifted to the left in nerves of affected dogs (E). See text for details

diameter of the enclosed axon was decreased, seemingly compressed by the Schwann cell changes, and an accumulation of organelles was present in the axoplasm, suggestive of axonal degeneration (Figure 4B-D). Some of organelles had double membranes and recognizable folding (cristae) of the inner membrane, indicating the presence of mitochondria.

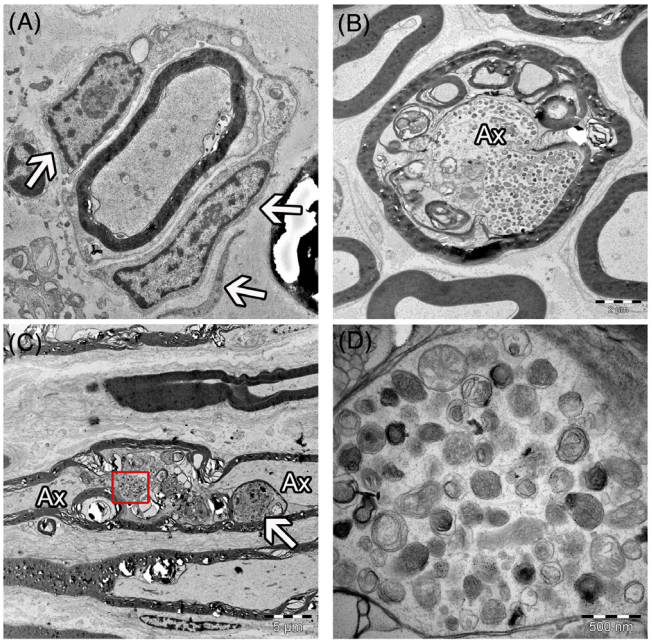

FIGURE 4 Transmission electron micrographs of the hypoglossal nerve of affected Alaskan malamutes. (A) Small onion bulbs, consisting of concentrically arranged supernumerary Schwann cells (A, arrows) around a thinly myelinated (remyelinated) axon, were present. (B, C [red frame magnified in D]) Folding of the inner part of the myelin sheath and pleomorphic material in the adaxonal part of the Schwann cell (C, arrow) were often observed, apparently compressing the axon (Ax). In the axoplasm, accumulations of organelles, including mitochondria, were present

No changes were observed in the tongue muscle (Figure 2A) and hypoglossal nerve (Figure 3B) of the control dog.

Morphometrical analyses of the hypoglossal nerve ($n = 3$) showed that a large proportion of the middle-sized axons in affected dogs had increased *g* ratio compared to the control dog, in accordance with the thinly myelinated fibers observed (Figure 3D). In a myelinated fiber diameter-frequency histogram the distribution was shifted toward lower diameter fibers in affected dogs (Figure 3E). Furthermore, *g* ratio/axon diameter scatter plot demonstrated a large proportion of nerve fibers with low *g* ratio and small axonal diameter in affected dogs, representing the previously described fibers with basophilic material adaxonally. As previously described,[5] the inclusion material in these fibers frequently is dispersed between dyscompacted myelin lamellae and the axonal diameter is small, despite an overall increase in nerve fiber diameter.

4 | DISCUSSION

Herein we describe tongue atrophy in Alaskan malamutes with AMPN as a novel clinical finding related to inherited polyneuropathy. Tongue atrophy was present in all affected dogs. Abnormal tongue appearance in the form of atrophy has not previously been associated with inherited polyneuropathies in dogs. We consider the observed changes in the tongue to be caused by neurogenic muscle atrophy. Spontaneous mutations in *NDRG1* causing degenerative polyneuropathy previously have been described in various mammalian species such as humans with CMT4D,[7] rodents (*stretcher* mouse),[14] dogs such as Greyhounds of show type[15]; and Alaskan malamutes.[4] Clinical signs differ slightly among the species but all display signs consistent with polyneuropathy involving the motor fibers of the nerves. Interestingly, tongue atrophy in species with *NDRG1* mutations causing polyneuropathy previously has only been described briefly in humans with CMT4D.[10] However, it also has been described as a rare clinical sign in a few other neuromuscular diseases in humans such as familial amyloid polyneuropathy[16] and myasthenia gravis (MG).[17-19] Unfortunately, no histopathology reports, diagnostic imaging results, photographs or results from electrodiagnostic examinations of the tongue muscle or hypoglossal nerve in humans affected with CMT4D are available. Likewise, no reports describe the age of onset, clinical course or clinical problems potentially associated with the tongue atrophy. Clinical signs of tongue atrophy are not reported in Greyhounds with polyneuropathy or in the *stretcher* mouse. Although, because of other predominating neurological signs such as general weakness and ataxia, tongue appearance might go unrecognized. In our study, the histopathologic findings of atrophy in the tongue musculature and degeneration of nerve fibers in the hypoglossal nerve resembled previously reported changes in other skeletal muscles and nerves of dogs diagnosed with AMPN.[5] Morphometrical assessment further supports the morphological changes, and is comparable to descriptions from other nerves in affected dogs with left-shifted diameter distribution of myelinated nerve fibers and increased *g* ratio.[5]

During the general physical examination of dogs, the tongue might be difficult to evaluate properly when not extended outside of the mouth. However, if overlooked, disease processes could easily be missed. Our study emphasizes the importance of a thorough tongue examination. Alterations in the appearance of the tongue could indicate a polyneuropathy that should be investigated further. Neither the clinical examination nor the disease history identified any overt clinical problems associated with tongue atrophy in the included dogs. However, taking into account the important role of the tongue in the swallowing process and the fact that dysphagia is described in human patients with hypoglossal palsy,[20] it cannot be ruled out that tongue atrophy might eventually cause clinical problems in dogs as well.

In humans, age-related tongue atrophy is reported in which a progressive increase of fat tissue occurs with a concomitant atrophy of muscle fibers. Thus, tongue volume and form are mainly unchanged, probably because of fat tissue replacement.[21] In the tongue of dogs with AMPN, fat cells do not seem to replace atrophic and sometimes necrotic myofibers, leading to collapse of the tissue structure and the macroscopic changes observed. Furthermore, endomysial fibrosis was observed and could contribute to contraction of the tissue, resulting in wrinkling of the tongue surface. The lack of fatty infiltration in the aged control dog also suggests that dogs generally are less prone to accumulate fat in the tongue compared with humans, and that the severe neurogenic muscle atrophy in AMPN dogs is unlikely to be

masked by fat cells replacing atrophic myofibers. In the peripheral nerves of dogs, age-associated changes may be expected at an age of 10 years or older.[22] All dogs in our study population were below this age when necropsy was performed. Therefore, it is less likely that age-related changes were the underlying cause of the histopathologic changes observed in the hypoglossal nerve. In addition, no changes in the tongue muscle or other changes in the hypoglossal nerve were identified in the control dog. Considering that axonal degeneration was present in the hypoglossal nerve, it seems most likely that the muscle atrophy was a result of denervation.

The muscle fibers in the tongue muscle had a characteristic pattern of increased variation in muscle fiber diameter caused by atrophy and hypertrophy of muscle fibers. In addition, several of the hypertrophic fibers contained internal nuclei, which suggests a chronic lesion.[23] In healthy muscles, muscle fibers belonging to 1 motor unit intermingle with muscle fibers from other units. Thus, in mild denervation where only a few motor units are affected, the denervated muscle fibers will become atrophic and compressed by neighboring fibers, resulting in an angular shape. More severe denervation results in groups of round, atrophic fibers. Both patterns were observed in the tongues of affected dogs. The finding of extensive small and large group atrophy, as well as hypertrophic fibers, indicates denervation as the cause of the muscle atrophy.[24] Long-term denervation can cause necrosis of muscle fibers,[25] thus explaining the focal areas of necrosis observed in 2 of the affected dogs. Needle insertion during EMG may induce needle myositis, which is a focal myositis with necrosis and phagocytosis.[26] However, EMG of the tongue was not performed in the 2 dogs in which necrosis was observed and cannot have resulted in these lesions. Taken together, the histopathologic changes of the tongue muscle resembled previously reported changes in other skeletal muscles (cranial tibial, biceps femoris and gastrocnemius muscles) in dogs with AMPN.[5] Electron microscopy of the hypoglossal nerves also identified changes similar to those previously described in other nerves of affected dogs,[5] indicative of a demyelinating polyneuropathy with secondary axonal degeneration. It is reasonable to conclude that the observed tongue atrophy is a consistent clinical sign of AMPN.

Four of 6 of the affected dogs in our study were tested for AChR ab with negative results. As previously mentioned, tongue atrophy is described as an abnormal finding in humans with MG, which recently has been associated with muscle-specific tyrosine kinase antibodies (MuSK-abs).[19] In dogs, at present there is no commercially available test for MuSK-abs and the prevalence of MuSK-abs associated MG is therefore unknown. However, all of the affected dogs were homozygous for a mutation in *NDRG1* and had histopathological changes indicative of a peripheral neuropathy, most likely explaining the tongue atrophy in these cases. Hypothyroidism may result in neuromuscular signs by causing neuropathy[27] or myopathy.[28] However, all of the included dogs had serum fT4, TT4, and TSH concentrations within the reference interval.

Electromyography of the tongue was performed in 2 of the affected dogs in our study. Moderate spontaneous activity was identified in both dogs, which is consistent with EMG findings in other skeletal muscles in dogs with AMPN.[3]

Hereditary polyneuropathies are reported in several dog breeds.[29] To date, tongue atrophy is not described in other dog breeds with inherited polyneuropathies. Therefore, we suggest that thorough tongue examination be performed in all dogs suspected of inherited polyneuropathy.

Our study had several limitations. First, the small sample size renders the clinical relevance of tongue atrophy in dogs with AMPN uncertain. However, tongue atrophy was present in all AMPN-affected dogs presented to the Small Animal Teaching Hospital during the study period. Second, the criteria for evaluation of tongue appearance are not well described in dogs, and the tongue appearance therefore was subjectively assessed in all dogs. However, the histopathological changes confirmed the observed macroscopic tongue atrophy in all affected dogs necropsied in our study.

In conclusion, clinical tongue atrophy is part of the disease phenotype of AMPN, mirroring histopathological alterations in both tongue musculature and hypoglossal nerves. The macroscopic tongue atrophy is considered neurogenic. When tongue atrophy is present, a thorough examination should be carried out to investigate for potential polyneuropathy. We also encourage clinicians to examine the tongue thoroughly for clinical signs of atrophy in dogs diagnosed with other polyneuropathies.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

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