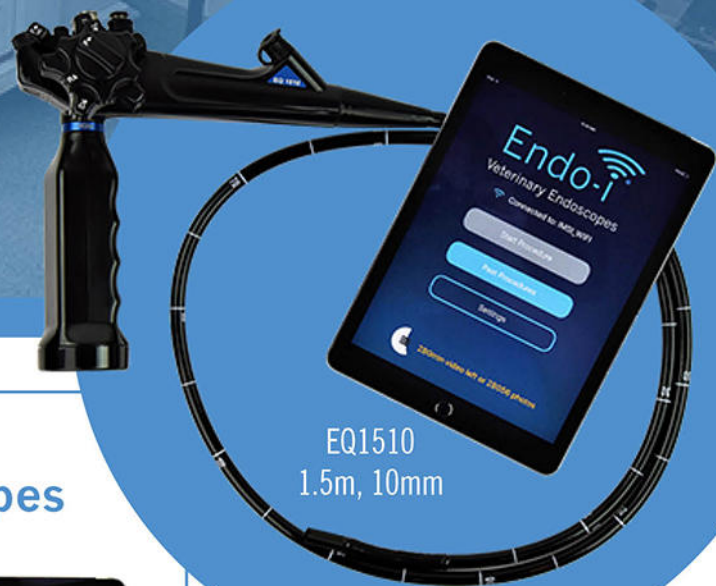


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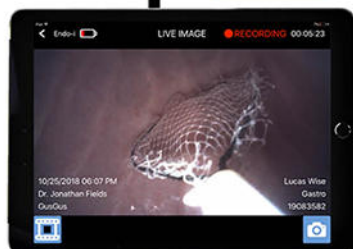
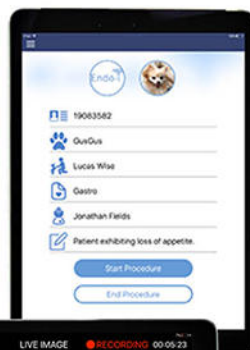
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STANDARD ARTICLE

Clinical findings and outcome of dogs with unilateral masticatory muscle atrophy

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Background: Little is known about the spectrum of underlying disorders in dogs with unilateral masticatory muscle (MM) atrophy.

Objectives: To evaluate the clinical presentation, magnetic resonance imaging (MRI) findings, and outcome of dogs with unilateral MM atrophy.

Animals: Sixty-three client-owned dogs.

Methods: The medical database was retrospectively reviewed for dogs that underwent MRI for evaluation of unilateral MM atrophy. Imaging studies were reviewed and follow-up information was obtained from telephone interviews.

Results: Presumptive trigeminal nerve sheath tumor (pTNST) was diagnosed in 30 dogs (47.6%); survival time varied from 1 day to 21 months (median, 5 months). Other extra-axial mass lesions were observed in 13 dogs (20.6%); survival time varied from 6 days to 25 months (median, 2.5 months). In 18 dogs (28.6%), no abnormalities were observed on MRI; neurological signs only progressed in 1 dog. Diagnosis had a significant influence on the type of neurological abnormalities, with additional neurological deficits observed in most dogs with pTNST and in all dogs with other extra-axial mass lesions. Diagnosis had a significant effect on euthanasia at the time of diagnosis and likelihood of neurological deterioration. Dogs with mass lesions were more likely to be euthanized or experience neurological deterioration, whereas these outcomes occurred less often in dogs in which no causative lesion could be identified.

Conclusions and Clinical Importance: Trigeminal nerve sheath tumors should not be considered the only cause of unilateral MM atrophy. Our results illustrate the importance of performing a neurological examination and MRI when evaluating dogs with unilateral MM atrophy.

KEYWORDS

cranial nerves, facial asymmetry, neuritis, trigeminal nerve sheath tumor

1 | INTRODUCTION

The muscles of mastication are responsible for movement of the mandible during prehension and mastication of food. They include the temporalis, masseter, pterygoideus, mylohyoideus, and digastricus muscles. The mandibular branch of the trigeminal nerve innervates each of these with the exception of the caudal belly of the digastricus,

which receives its innervation from the facial nerve.¹ Bilateral masticatory muscle (MM) atrophy occurs relatively commonly in dogs and can be caused by several underlying disease processes. Comparatively, facial asymmetry caused by unilateral MM atrophy is observed less frequently and is associated with a limited number of differential diagnoses.² Neoplasia of the trigeminal nerve is thought to be the most common cause of unilateral MM atrophy.^{2,3} By far the most common type of tumor affecting the trigeminal nerve is malignant nerve sheath tumor with other tumors, such as lymphoma, occurring less commonly.⁴ Trigeminal nerve sheath tumors (TNST) are an uncommon intracranial neoplasm in dogs, for which unilateral MM atrophy

Abbreviations: CSF, cerebrospinal fluid; MM, masticatory muscle; MRI, magnetic resonance imaging; PLR, pupillary light reflex; pTNST, presumptive trigeminal nerve sheath tumor; TNST, trigeminal nerve sheath tumor.

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appears to be a consistent clinical feature.³ The nature of additional clinical signs seen is reflected by the local effects of trigeminal nerve dysfunction and those secondary to potential brainstem compression. Reported findings in animals with TNST therefore include decreased facial sensation, facial rubbing, absent palpebral reflex, decreased corneal sensation, ocular pathology, decreased menace response, torticollis, ipsilateral Horner's syndrome, enophthalmia, and paradoxical vestibular syndrome.^{3,5-8} The auditory tube is controlled by the tensor tympani and tensor veli palatini muscles innervated by the trigeminal nerve and the levator veli palatini and salpingopharyngeus muscles innervated by the vagus nerve. Trigeminal nerve lesions therefore also have been associated with auditory tube dysfunction and middle ear effusion in dogs.⁹⁻¹¹ These neoplasms typically affect older dogs and are considered progressive.^{3,7,9} Other differential diagnoses for unilateral MM atrophy include neuropathies such as trigeminal neuritis,⁶ idiopathic trigeminal neuropathy,⁵ and also could include myopathies, traumatic injury, or extension of other extra-axial mass lesions.¹² To date, little is known about the spectrum, distribution, progression, and outcome of underlying causes for unilateral MM atrophy. Our aims therefore were to investigate the various etiologies, presenting signs, magnetic resonance imaging (MRI) findings, and outcome of dogs presenting with unilateral MM atrophy. The results of our study may help guide clinical investigations, as well as improve understanding of the disease progression both for accurate prognostication, treatment selection, and management of owner expectations.

2 | MATERIALS AND METHODS

The study was approved by the local clinical research ethical review board (URN: M2016 0088). The electronic medical databases of 2 academic referral hospitals were searched from June 2003 to October 2016 for dogs presented with unilateral MM atrophy as their predominant clinical sign. Dogs were included in the study if: (1) they were referred for further investigation of unilateral MM atrophy as the predominant clinical sign, (2) complete medical records were available for review, (3) facial asymmetry with unilateral MM atrophy was confirmed on clinical examination, and (4) MRI of the head was performed and images were available for review. Histopathological confirmation was not necessary to be included in this study. Information retrieved from

the clinical records included signalment, clinical signs, neurological examination findings, results of diagnostic investigations, and any treatment received. Dogs were excluded if clinical records or imaging studies were unavailable for review or if unilateral MM atrophy was incidentally observed or not the predominant clinical indication for referral. All medical files and imaging studies were reviewed by a board-certified neurologist (Steven De Decker) to evaluate if potential cases could be included or should be excluded. After reviewing the MRI studies, included dogs were divided into 4 diagnostic categories: (1) presumptive trigeminal nerve sheath tumor (pTNST); (2) other extra-axial mass lesions affecting the cerebellopontine angle or petrosal part of the temporal bone; (3) unilateral MM atrophy with no causative lesion identified on MRI; and (4) dogs that could not be classified into any of the above categories (Figure 1).

For the purpose of the study, pTNST was defined as a unilateral, well-circumscribed, extra-axial, homogeneously contrast-enhancing mass at the level of the pons, or associated with 1 or more branches of the trigeminal nerve within the caudal cranial fossa, middle cranial fossa, or in the extracranial peripheral division of its branches or both.^{3,6,9,11} Other extra-axial mass lesions affecting the cerebellopontine angle or petrosal part of the temporal bone, but not arising from the trigeminal nerve or ganglion, were classified in a separate group.

Magnetic resonance imaging of the head of each dog was performed under general anesthesia using a permanent 1.5T Magnet (Intera, Philips Medical Systems, Eindhoven, the Netherlands, or Siemens Magnetom Essenza, Frimley, United Kingdom). The MRI sequences included a minimum of T2-weighted (TW2; repetition time [TR] [ms], echo time [TE] [ms] 3333/110) sagittal and transverse images and transverse fluid attenuation inversion recovery images (FLAIR; TR/TE, 6000/120). Transverse plane T1-weighted (T1W) images (TR/TE, 515/15) were acquired before and after IV injection of gadolinium contrast material (0.1 mL/kg gadoterate meglumine, Dotarem, Guerbet, Milton Keynes, England). Slice thickness was 3.5 mm in all planes with an interslice gap of 0.9 mm in the sagittal and 1 mm in the transverse planes. Images of dogs with pTNST were reviewed by a board-certified neurologist (Elsa Beltran), who did not perform the initial evaluation of the imaging studies, using Osirix DICOM viewer (Osirix Foundation, V.5.5.2 Geneva, Switzerland). This reviewer was aware of the suspected diagnosis of pTNST in each case, but was blinded to the signalment, and general physical and neurological examination findings.

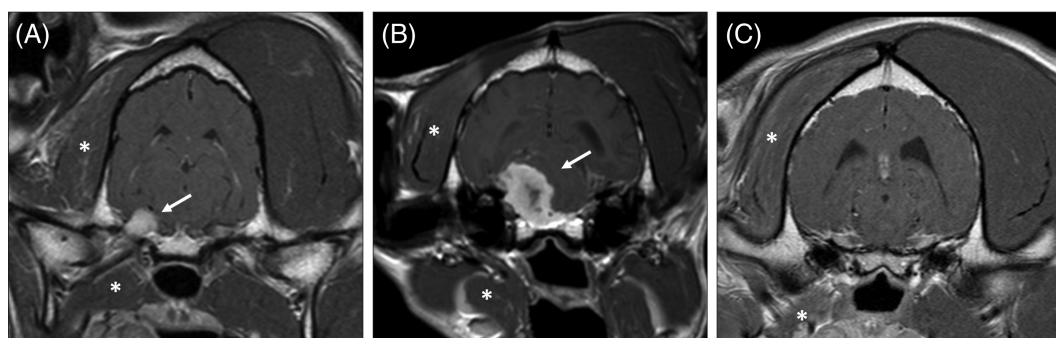


FIGURE 1 T1-weighted transverse images after IV administration of gadolinium contrast material in 3 dogs presenting for further evaluation of right-sided unilateral masticatory muscle atrophy. Atrophied muscles are indicated with asterisk. A, Presumptive trigeminal nerve sheath tumor (arrow). B, An extra-axial mass affecting the cerebellopontine angle (arrow). C, No abnormalities were detected on magnetic resonance imaging with the exception of unilateral masticatory muscle atrophy

The trigeminal nerve was evaluated using 5 variables as previously reported for oculomotor nerve dysfunction:¹³ (1) enlargement (mild or marked); (2) intensity on T2W and T1W images; (3) degree of contrast enhancement (none, mild, or marked); (4) pattern of contrast enhancement (focal or diffuse and homogenous or heterogeneous enhancement); and (5) anatomical region of the lesion. The presence of middle ear effusion was recorded for all included dogs.

Follow-up to discharge was collated from both referral centers, and subsequent follow-up from the referring veterinarian also was obtained. Initially, the referring veterinary surgeon of each animal was contacted by telephone. For dogs that were deceased, the date, cause of death, and last recorded neurological status at the time of death were recorded. In accordance with local ethical and welfare committee guidelines, owners of deceased dogs were not contacted further. For all dogs that were presumed to be still alive at the time of study enrollment, a letter was sent to the owner outlining the study aims along with a standardized questionnaire before being contacted for a telephone interview. Owners were asked to comment on neurological progression and improvement of clinical signs. Telephone interviews were performed by 1 of 2 investigators (Emily J. Milodowski for cases from the Royal veterinary College and PA-B for cases from Glasgow University). The questionnaire was approved by the local ethics and welfare committee (Supporting Information Questionnaire).

Statistical analysis was performed by commercial statistical software (GraphPad prism 7, Version 7.0a for Mac OS X, GraphPad Software, La Jolla, California). Dogs that were euthanized at the time of original diagnosis, or that were lost to follow-up, were censored from statistical analysis from the point of last contact. Overall survival time was calculated from the time of MRI diagnosis. Dogs in the unclassified group were excluded from statistical analysis. Data for age, duration of clinical signs, and survival time were assessed for normality by the Shapiro-Wilk normality test. Continuous data was compared by Kruskal-Wallis tests and categorical data were evaluated using chi-square or Fisher's exact tests. The occurrence of neurological abnormalities detected at the time of presentation was compared with a 2-way analysis of variance (ANOVA). A value of $P < .05$ was considered statistically significant. Significance level for multiple comparisons was adjusted by Bonferroni's method.

3 | RESULTS

Sixty-three dogs were included in the study. Unilateral MM atrophy was associated with pTNST in 30 dogs (47.6%), other extra-axial mass lesions affecting the cerebellopontine angle or petrosal part of the temporal bone in 13 dogs (20.6%), and no causative lesion was identified in 18 dogs (28.6%) and 2 dogs could not be classified into any of the above categories. Both of these cases presented with unilateral MM atrophy but neurological examination also identified sciatic neuropathy. The relationship between both conditions was unknown.

3.1 | Dogs with suspected TNST

The 30 dogs diagnosed with pTNST included 14 female (7 neutered) and 16 male (8 neutered) dogs. The median age at presentation was

9 years 3 months (range 1 year 6 months to 13 years). Breeds included Labrador Retriever ($n = 5$), Boxer, English Bull Terrier, West Highland White Terrier, Staffordshire Bull Terrier ($n = 2$ for each); 11 breeds were represented by 1 dog and 6 dogs were crossbreeds.

Left-sided unilateral MM atrophy was seen in 17 dogs and right-sided atrophy in 13 dogs. Duration of clinical signs varied from 10 days to 2 years before presentation (median, 2.75 months). Masticatory muscle atrophy was the only clinical sign in 5 dogs. Neurological examination identified additional abnormalities in the remaining 25 dogs (83%) and included enophthalmos ($n = 12$ dogs), facial hyperesthesia ($n = 2$), decreased or absent ipsilateral palpebral reflex ($n = 10$), head tilt ($n = 6$) opposite to the side of MM atrophy in 2 dogs, generalized ataxia ($n = 6$), proprioceptive deficits ($n = 6$), cervical hyperesthesia ($n = 6$), obtundation ($n = 5$), decreased ipsilateral menace response ($n = 5$), positional strabismus ($n = 5$), ipsilateral Horner's syndrome ($n = 4$), decreased gag reflex ($n = 4$), decreased pupillary light reflex (PLR; $n = 1$), nystagmus ($n = 1$), and tetraparesis ($n = 1$). A Schirmer's tear test identified decreased tear production in 2 dogs. Magnetic resonance imaging disclosed middle ear effusion in 18 dogs (60%). The effusion was ipsilateral to the MM atrophy in 16 dogs, whereas bilateral effusion was observed in 2 dogs. The MRI appearance of the pTNSTs was recorded (Table 1). In 9 of 30 dogs, cerebrospinal fluid (CSF) analysis using CSF from cisternal puncture was performed; total nucleated cell count was normal ($<5/\mu\text{L}$) in all samples, but 2 dogs showed increased CSF protein concentrations (0.49 g/L and 0.54 g/L; reference interval, <0.3 g/L).

Three dogs were euthanized at the time of diagnosis without treatment attempted because of the severity of clinical signs and anticipated poor prognosis. Nine of the remaining 27 dogs did not receive any specific treatment. Treatment in the remaining 18 dogs varied and included prednisolone alone ($n = 8$ dogs); prednisolone in combination with radiotherapy ($n = 2$) or gabapentin ($n = 1$); meloxicam with cyclophosphamide ($n = 2$); meloxicam alone ($n = 1$); hydroxyurea alone ($n = 3$); and hydroxyurea in combination with

TABLE 1 Magnetic resonance imaging characteristics of 30 dogs diagnosed with presumptive trigeminal nerve sheath tumor

Evaluated variable	Finding	Number of dogs
Trigeminal nerve enlargement	Marked	23
	Mild	7
Position	CCF + TC + MCF + EC	18
	CCF + TC + MCF	6
	TC + MCF	3
	TC + MCF + EC	2
	MCF	1
T2-weighted intensity	Hyperintense	20
	Isointense	9
	Hypointense	1
T1-weighted intensity	Isointense	17
	Hypointense	13
Contrast enhancement	Marked	23
	Mild	7

Abbreviations: CCF, caudal cranial fossa; EC, extra-cranial portion; MCF, middle cranial fossa; TC, trigeminal canal.

lomustine ($n = 1$). Outcome data were available for 22 of the 27 dogs. Twenty-one of these 22 dogs were dead at the time of study enrollment, whereas 1 dog was still alive despite progression of vestibular signs 7 months after diagnosis. Two dogs were euthanized in the first 7 days after treatment was initiated. They were euthanized because of progression of clinical signs, and both had received prednisolone after diagnosis. Seventeen other dogs were euthanized between 9 days and 24 months (median, 8 months) after diagnosis of pTNST because of continuous progression of neurological signs. Progression of neurological signs included development of vestibular signs in 13 dogs, loss of facial sensation ($n = 5$), loss of corneal reflex ($n = 3$), collapse episodes ($n = 2$), seizures ($n = 2$), Horner's syndrome ($n = 2$), decreased gag reflex and dysphagia ($n = 2$), obtundation ($n = 1$), tongue deviation ($n = 1$), and cervical hyperesthesia ($n = 1$). Two dogs were euthanized for unrelated causes, 1 because of developing persistent blindness after cataract surgery 5 months after diagnosis, the other because of severe osteoarthritis 21 months after diagnosis. Neither dog was reported to have experienced neurological deterioration after diagnosis. For the purpose of the study, these 2 dogs were included in the survival analysis. Overall survival time for this group varied from 1 day to 1 year and 9 months after diagnosis (median 5 months).

3.1.1 | Dogs with other extra-axial mass lesions affecting the cerebellopontine angle or petrosal part of the temporal bone

Of the 13 dogs with other extra-axial mass lesions, 6 were females (3 neutered) and 7 were neutered males. Median age at diagnosis was 7 years 5 months (range 5 years 1 month to 11 years 5 months). This group included 2 Labrador Retrievers, 2 Boxers, 5 breeds were represented by 1 dog, and 4 dogs were cross breeds. The duration of clinical signs varied from 2 weeks to 1 year (median 1 month). Six dogs had left-sided and 7 dogs had right-sided MM atrophy. All dogs (100%) had additional abnormalities on neurological examination including decreased palpebral reflex ($n = 5$ dogs), head tilt ($n = 5$), which was toward the affected side in 4 dogs, generalized ataxia ($n = 5$), decreased mentation ($n = 4$), decreased tear production ($n = 4$), proprioceptive deficits ($n = 4$), decreased menace response ($n = 3$), Horner's syndrome ($n = 3$), decreased corneal reflex ($n = 2$), strabismus ($n = 2$), cervical hyperesthesia ($n = 2$), nystagmus ($n = 2$), ipsilateral facial hyperesthesia ($n = 1$), and abnormal PLR ($n = 1$). Two dogs had corneal ulceration.

Assessment of MRI indicated extra-axial mass lesions ipsilateral to the MM atrophy, which did not arise from the trigeminal nerve or ganglion. In 9 cases, an extra-axial homogeneously contrast-enhancing mass lesion was located in the cerebellopontine angle. The most likely differential diagnoses for these dogs were considered to be meningioma and histiocytic sarcoma. Histopathological examination resulted in a diagnosis of histiocytic sarcoma in 1 dog. In the remaining 4 cases, the lesion affected primarily the petrosal portion of the temporal bone. The most likely differential diagnosis for these 4 dogs was considered to be a tumor of bone, such as osteosarcoma. Four cases (31%) were observed to have ipsilateral middle ear effusion. In 1 dog, CSF analysis using CSF from cisternal puncture was performed, and the results were within normal limits.

Six dogs were euthanized at the time of diagnosis without treatment because of the nature of the diagnosis and severity of clinical signs. Follow-up data were available for 6 of the remaining 7 cases. One dog did not receive any specific type of treatment and was euthanized 6 days after diagnosis because of progression of clinical signs. Three dogs were treated with prednisolone alone; 1 was euthanized after 7 days, 1 survived for 2 months, and the remaining dog survived for 6 months after diagnosis. All 3 dogs experienced progression of neurological signs before euthanasia, including deterioration in mentation and vestibular signs. One dog was treated with a combination of prednisolone, hydroxyurea, and lomustine. This dog was euthanized 3 months later because of progression of tetraparesis and generalized ataxia. The final dog was treated with a combination of prednisolone, hydroxyurea, and radiotherapy. This dog experienced neurological deterioration beginning 6 months after diagnosis. The dog developed Horner's syndrome, decreased facial sensation, and head tilt, and was euthanized 25 months after diagnosis. Overall survival time for this group varied therefore from 6 days to 25 months after diagnosis (median, 2.5 months).

3.1.2 | Dogs without an underlying lesion detected on MRI

In 18 of the 63 dogs, no identifiable lesion was detected on MRI of the head except for unilateral MM atrophy. This group consisted of 14 males (4 neutered) and 4 females (2 neutered). Median age at diagnosis was 7 years 10 months (range, 2 years 10 months to 11 years 1 month). Breeds included Staffordshire Bull Terrier ($n = 5$ dogs), Labrador Retriever ($n = 4$), 7 breeds were represented by 1 dog, and 2 dogs were cross breeds. Twelve dogs had left-sided and 6 had right-sided MM atrophy. Duration of clinical signs before presentation varied from 1 day to 1 year (median, 2 months). In 9 dogs, facial asymmetry as a result of MM atrophy was the only clinical sign detected. Neurological examination disclosed additional abnormalities in the remaining 9 dogs (50%) and included Horner's syndrome ($n = 5$ dogs), decreased or absent facial sensation ($n = 3$), decreased corneal sensation ($n = 2$), decreased palpebral reflex ($n = 2$), and decreased menace response ($n = 1$). A Schirmer's tear test identified decreased tear production in 1 dog.

Assessment of MRI findings indicated middle ear effusion in 3 dogs; 1 dog had bilateral effusion, 1 dog had ipsilateral effusion, whereas the effusion was contralateral to the MM atrophy in the 3rd dog. In 12 dogs, CSF analysis using CSF obtained by cisternal puncture was performed; total nucleated cell count was mildly increased in 1 case (8 cells/ μ l; reference interval, <5 cells/ μ l). In 1 dog, CSF protein concentration was increased with normal cell count (0.62 g/L; reference interval, <0.3 g/L). Electromyography was performed in 4 dogs and disclosed positive sharp waves in the affected muscles, but no abnormalities were seen in unaffected muscles. Testing for type 2M antibodies was performed in 8 dogs, including the 4 dogs that underwent electromyography. All had negative results.

One dog was euthanized at the time of diagnosis at the owner's request because of a potentially poor prognosis. This dog also had decreased facial sensation, loss of palpebral reflex, and ipsilateral Horner's syndrome. Of the remaining 17 dogs, 9 received treatment and 8 did not receive treatment. Treatment included prednisolone alone

($n = 4$ dogs), prednisolone in combination with cyclophosphamide ($n = 1$), gabapentin ($n = 1$), gabapentin and radiotherapy ($n = 1$), or hydroxyurea alone ($n = 1$). One dog received a combination of neomycin, polymyxin, and dexamethasone ophthalmic ointment and cyclosporine A ointment for ocular pathology and decreased tear production, but no further treatment specifically related to MM atrophy. Four dogs were lost to follow-up and of the remaining 13 dogs, 8 were dead (median survival time, 25 months; range, 7 days to 65 months), and 5 remained alive at the time of study enrollment (at 18, 33, 35, 36, and 54 months after diagnosis). Of the dogs that were dead, only 1 was euthanized because of neurological disease. This dog did not experience progression of clinical signs after diagnosis until developing progressively decreased mentation and nonambulatory tetraparesis 38 months after diagnosis. No further diagnostic tests were performed before euthanasia and this dog was treated with prednisolone, gabapentin, and radiotherapy after diagnostic tests for unilateral MM atrophy were performed. It is therefore unclear if this dog was euthanized for reasons related to the initial presentation of unilateral MM atrophy. The remaining 7 dogs died or were euthanized for unrelated reasons without further progression of neurological signs.

Of the 5 dogs still alive at the time of data collection, none had experienced progression of neurological signs. In 2 dogs, the MM atrophy resolved without treatment. Another dog retained persistent stable facial asymmetry after discharge. In the 2 remaining dogs, unilateral MM muscle atrophy progressed after initial clinical presentation. One of these dogs did not receive any treatment, whereas the other dog developed bilateral MM atrophy while being treated with prednisolone.

3.2 | Dogs that could not be classified into groups

Two dogs were presented with unilateral MM atrophy and concurrent sciatic neuropathy of the contralateral limb. No abnormalities of the lumbosacral area, trigeminal nerves, cerebellopontine area, or petrosal part of the temporal bone were identified on MRI. The 1st dog was a 7-year 1-month-old male neutered cross breed, and improved with treatment using gabapentin and meloxicam. The dog was alive at the time of data collection, 47 months after diagnosis. The 2nd dog was an 8 year 2-months-old male intact Labrador Retriever. This dog received multiple treatments with vincristine, cyclophosphamide, prednisolone, and cytosine arabinoside because of suspected lymphoma. Resolution of unilateral MM atrophy was recorded over 12 months, but sciatic deficits were reported persistently over the next 3 years. This dog was euthanized 50 months after diagnosis. Necropsy identified generalized peripheral neuropathy, with the right sciatic nerve most affected. No inflammatory or neoplastic cells were detected in the trigeminal or sciatic nerve.

3.3 | Comparison between groups

Diagnosis had a significant influence on the type of abnormalities detected on neurological examination. Dogs with other extra-axial mass lesions had head tilt and ataxia significantly more often ($P = .02$ for both) compared to dogs without an underlying cause identified on MRI. No significant differences were observed between both groups

(dogs with other extra-axial mass lesions and dogs in which no abnormalities were detected) and dogs with pTNST ($P > .05$). Diagnosis had a significant influence on the occurrence of middle ear effusion ($P = .008$). Dogs with pTNST were more likely to have middle ear effusion compared to dogs with no causative lesion observed on MRI ($P = .003$). No significant differences were found between dogs with other extra-axial mass lesions and dogs with pTNST or between dogs with other extra-axial mass lesions and dogs in which no causative lesion was observed on MRI ($P > .05$). Diagnosis significantly influenced whether or not treatment was attempted ($P = .004$). Dogs diagnosed with other extra-axial mass lesions were more likely to be euthanized at the time of diagnosis compared to either the pTNST group ($P = .01$) or those with no causative lesion identified on MRI ($P = .01$). No significant difference was found between dogs with pTNST and those in which no underlying cause could be identified ($P > .05$). Diagnosis significantly influenced the likelihood of neurological deterioration after diagnosis ($P = .0007$). Neurological deterioration occurred significantly less often in dogs in which no causative lesion could be identified on MRI compared to dogs with pTNST ($P = .006$) and other extra-axial mass lesions ($P = .003$). No significant difference was found for the likelihood of neurological deterioration between dogs with pTNST and other extra-axial mass lesions. Diagnosis did not have a significant influence on any of the other evaluated variables ($P > .02$; Bonferroni correction for multiple comparisons).

4 | DISCUSSION

We evaluated the spectrum of clinical characteristics, progression, and outcome of different underlying causes of unilateral MM atrophy in dogs. Our results indicate that pTNST should be considered the most common cause of unilateral MM atrophy, representing almost half of the dogs included in this study, but other diagnoses constituted over half of the cases. These included other extra-axial masses not arising from the trigeminal nerve, whereas in 28.6% of cases no causative lesion was observed on MRI studies of the head. This finding suggests that, although an important differential diagnosis, TNST should not be considered the only cause of unilateral MM atrophy. Our results further suggest that unilateral MM atrophy can be caused by a variety of underlying benign and malignant conditions. This finding emphasizes the importance of making as accurate as possible a diagnosis by performing a complete neurological examination in combination with advanced diagnostic imaging in dogs presenting with unilateral MM atrophy. Although all included dogs were presented with unilateral MM as their predominant clinical sign, neurological examination identified additional abnormalities in most dogs with pTNST and in all dogs with other extra-axial mass lesions. Signs of intracranial involvement including head tilt, ataxia, proprioceptive deficits, and obtundation commonly were reported in these groups of dogs. Alternatively, in half of dogs with no causative lesion observed on MRI, neurological examination did not identify any additional abnormalities, and neurological deficits always were limited to the trigeminal nerve or neural structures in close proximity of the trigeminal nerve, such as the sympathetic or facial nerve. Intracranial signs such as head tilt, ataxia,

proprioceptive deficits, or obtundation were not observed in this group of dogs.

As expected, pTNST was the most common cause of unilateral MM atrophy in our study population. Observed clinical signs, neurological deficits, and MRI findings were similar to those previously reported.^{3,7,9} Although recent studies have focused on clinical outcomes after advanced treatment strategies, including stereotactic radiotherapy^{7,9} and volumetric-modulated arc radiotherapy,¹⁴ the natural progression and survival of dogs with TNST after conservative treatment has rarely been reported. Although 2 of 27 dogs in which treatment was attempted underwent radiotherapy, the remaining 25 dogs included in our study received conservative medical treatment or no specific treatment at all. The median survival time of 4 dogs treated conservatively was 12 months in 1 study (range, 5-21 months),³ whereas the median survival time of 10 dogs was only 12 days in a more recent study (range, 1-577 days), with 40% of conservatively treated dogs being alive at 1 year after diagnosis.⁹ In agreement with these findings, the median survival time in our study was 5 months and ranged from 1 day to 21 months. In agreement with previous reports, reliable assessment of outcome was complicated by variation in clinical presentation, MRI findings, and type of medical management, and also because several dogs were euthanized at the time of or soon after diagnosis.^{3,9} Although the prognosis of dogs with pTNST is poor, it is difficult to accurately predict the outcome and survival time of dogs treated conservatively for pTNST. In agreement with previous studies,^{7,9} progression of clinical signs was characterized by progressive brainstem compression or other central nervous system signs, such as vestibular signs, multiple cranial nerve deficits, seizures, or obtundation.

Our results suggest that other extra-axial mass lesions affecting the cerebellopontine angle or petrosal portion of the temporal bone should be considered as important differential diagnoses for unilateral MM atrophy in dogs. Lesions producing trigeminal motor nerve dysfunction and subsequent MM atrophy may occur anywhere along the course of the trigeminal nerve from its motor nucleus in the pons to its distal peripheral nerve endings. The motor nucleus of the trigeminal nerve is found at the level of the middle and rostral cerebellar peduncles just rostral to where the cerebellar peduncles merge with the cerebellum. After the trigeminal motor neurons exit the pons, they pass into the canal of the trigeminal nerve in the petrosal portion of the temporal bone where the trigeminal ganglion also is located.¹ Thus, lesions affecting the cerebellopontine angle or petrosal portion of the temporal bone can cause MM atrophy.

Although unilateral MM atrophy often is caused by conditions associated with a poor prognosis, MRI did not identify a lesion in >25% of our cases. Magnetic resonance imaging did not show any abnormalities in the pons or along the anatomical pathway of the trigeminal nerve. It is unclear whether or not dogs in this group all were affected by the same underlying pathology or a more heterogeneous group of disorders. Potential underlying conditions could be inflammatory, traumatic, neoplastic, degenerative, or idiopathic in nature. Although Staffordshire Bull Terriers and Labrador Retrievers most often were affected by this clinical presentation, it is unclear if a true breed predisposition exists. Unilateral MM atrophy theoretically could be caused by disorders affecting the trigeminal nerve or the MMs themselves, such

as masticatory myositis.^{2,15} In half of affected cases, neurological examination did however identify abnormalities suggestive of dysfunction of other branches of the trigeminal nerve or dysfunction of neural structures in close proximity to the trigeminal nerve. Additionally, testing for type 2M antibodies indicative of masticatory myositis was negative in all tested cases. These findings could suggest that unilateral MM atrophy without abnormalities observed on MRI could represent a neuropathy instead of a myopathy in some cases. Unilateral MM atrophy as the sole clinical sign in combination with normal MRI findings is a rare clinical presentation in humans.¹⁶⁻¹⁸ This presentation is considered benign and is referred to as pure trigeminal motor neuropathy. It is characterized by trigeminal motor paralysis without sensory trigeminal disturbances or involvement of other cranial nerves.¹⁶⁻¹⁸ Although this clinical presentation is similar to that observed in the dogs of our study, several animals had clinical signs suggestive of trigeminal sensory neuropathy and involvement of cranial nerves in close proximity to the trigeminal nerve. It is possible that MRI was not sensitive enough to detect small lesions along the anatomical pathway of the trigeminal nerve. Thus, it remains uncertain if unilateral MM atrophy in dogs without abnormalities on MRI represents a benign or malignant condition. This uncertainty is reflected by the fact that 1 dog was euthanized at the time of diagnosis, approximately half of the dogs did not receive any specific type of treatment, and a variety of treatments were recommended in the remaining dogs. With the exception of 1 dog, neurological deterioration was not observed in any of the dogs in which MRI failed to identify an underlying cause for unilateral MM atrophy. The dog that was euthanized for neurological deterioration had received radiotherapy and developed decreased mentation and nonambulatory tetraparesis 38 months after MRI was performed. Unfortunately, no further diagnostic tests were performed at the time of euthanasia. This dog may have developed neurological signs because of trigeminal nerve pathology, but it also is possible that this dog could have developed an unrelated neurological disorder or suffered from late effect radiation toxicity, which is characterized by persistent progressive neurologic signs >6 months after radiation treatment without imaging evidence of tumor progression.¹⁹ It remains unclear if this dog was euthanized for reasons related or unrelated to its clinical presentation for unilateral MM atrophy. A study evaluating the outcome of dogs with suspected TNSTs after stereotactic radiotherapy suggested that late radiation effects cannot always be distinguished from tumor progression.⁷ Most of the remaining treated dogs received prednisolone with or without additional chemotherapy. It can be questioned however if: (1) medical treatment is necessary in these dogs, (2) benefits of empirical medical treatment outweigh costs and potential adverse effects; and (3) if treatment with prednisolone complicates assessment of clinical progression. The adverse effects of prednisolone are well characterized and include muscle atrophy, which often predominantly affects the temporalis muscles.^{20,21} For these reasons and because none of the dogs that did not receive medical treatment experienced progression of neurological deficits, we currently do not recommend starting empirical treatment when MRI does not identify an underlying cause for unilateral MM atrophy.

Our study had several limitations. Although previously published imaging criteria were used, diagnoses were not confirmed by histopathology. It has been determined previously that histopathology is required for accurate diagnosis because the MRI appearance of TNST

can be mimicked by nonneoplastic conditions such as trigeminal neuritis.²² Assessment of outcome was complicated by the fact that some clients elected euthanasia without attempting further treatment, by variation in treatment protocols for the remaining dogs, by variable clinical presentations, and by different imaging findings among dogs within the same diagnosis category. Assessment of outcome was further complicated by the retrospective nature of the study. Only dogs assessed for further evaluation of facial asymmetry caused by unilateral MM atrophy were included. Dogs that had unilateral MM atrophy as part of a more complex clinical presentation were not included. Our study therefore does not include all possible underlying causes for unilateral MM atrophy in dogs, but rather those disorders associated with unilateral MM atrophy as a predominant clinical sign.

Despite these limitations, our study had several new clinically relevant findings. Unilateral MM atrophy is an uncommon clinical presentation associated with facial asymmetry, altered facial aesthetics, and a variable prevalence of additional neurological deficits. Historically, unilateral MM atrophy has been associated with a poor prognosis and has been assumed to be most commonly caused by trigeminal nerve neoplasia. Although our study confirmed that pTNST was the most common cause, unilateral MM atrophy is not pathognomonic for PNST and alternative etiologies are implicated in >50% of cases. More than 25% of dogs with unilateral MM atrophy have no lesions detected on MRI and generally do not experience further disease progression. Although additional studies are necessary to determine the underlying pathology in this last group of dogs, this finding illustrates that unilateral MM atrophy can be caused by a variety of malignant and benign conditions. This observation emphasizes the importance of performing a complete neurological examination and advanced diagnostic tests in dogs presenting with unilateral MM atrophy.

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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

This study was approved by the Royal Veterinary College clinical research ethical review board (URN: M2016 0088).

HUMAN ETHICS APPROVAL DECLARATION

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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