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Facial Myokymia With or Without Concurrent Neurological Deficits in Seven Dogs and Two Cats

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ABSTRACT

Background: Myokymia is a form of peripheral nerve hyperexcitability that can be focal or generalized. Information regarding focal myokymia in veterinary medicine is currently limited, resulting in a need for a better understanding of this clinical sign.

Hypothesis/Objectives: Describe the clinical presentation, diagnostic findings, treatment, and outcomes in dogs and cats with facial myokymia (FM).

Animals: Seven dogs and two cats with clinically confirmed FM.

Methods: Retrospective study. Clinical records from six referral institutions were reviewed to identify cases with FM. Signalment, clinical presentation, diagnostic test results, treatment, and outcome were recorded and evaluated for each patient.

Results: Facial myokymia was detected before referral in 6/9 cases. Concurrent vestibular signs were present in 7/9 cases, whereas signs of facial nerve dysfunction other than FM were present in three cases. The diagnoses in the seven dogs were facial and vestibular neuropathy of unknown etiology ($n = 2$), extra-axial neoplasia ($n = 1$), otitis media-interna with intracranial extension ($n = 1$), otitis interna with associated facial and vestibulocochlear neuropathy ($n = 1$), meningoencephalitis of unknown origin ($n = 1$) and neoplasia or hypertrophic neuritis ($n = 1$). The two cats were diagnosed with retrobulbar adenosquamous carcinoma with intracranial extension and traumatic orofacial injury. When prednisolone was used (6/9 cases) FM improved or resolved, although relapses were common.

Conclusions and Clinical Importance: Facial myokymia is an uncommon and nonspecific clinical sign in dogs and cats, associated with a range of structural disorders affecting the facial motor nucleus, nerve, or both. Control of FM is variable, and treatment and outcome depend on the underlying cause.

Abbreviations: ACD, albuminocytologic dissociation; BoNT-A, botulinum neurotoxin type A; CNS, central nervous system; CSF, cerebrospinal fluid; EMG, electromyography; FM, facial myokymia; FVNUE, facial and vestibular neuropathy of unknown etiology; GA, general anesthesia; MRI, magnetic resonance imaging; MS, multiple sclerosis; MUO, meningoencephalitis of unknown origin; PCR, polymerase chain reaction; PNH, peripheral nerve hyperexcitability.

1 | Introduction

Myokymia and neuromyotonia are related clinical phenomena that result from hyperexcitability of peripheral nerve motor axons, with neuromyotonia being a more severe form of myokymia [1]. Both may occur in generalized or focal forms and reflect a generalized or focal alteration in the microenvironment or membrane of the peripheral nerve [1]. Myokymia represents an involuntary, spontaneous, and continuous rippling contraction of facial or limb myofibers, often presenting as an undulation or vermicular (worm-like) movement of the skin overlying the affected muscle [2]. In veterinary medicine, generalized myokymia and neuromyotonia have been well characterized in Jack Russell Terriers and related breeds [3].

In addition to myokymia and neuromyotonia, other clinical signs described in affected dogs are spinocerebellar ataxia and epileptic seizures [3]. A missense mutation in the gene *KCNJ10* was identified as the cause of the spinocerebellar ataxia, but the direct association between this variant and myokymia and neuromyotonia remains to be clarified [4]. Generalized myokymia and neuromyotonia also have been reported in a cat [5]. Focal myokymia has only been reported in four dogs: one with palatolingual myokymia and a pituitary adenoma [6], one with myokymia in a pelvic limb secondary to radiation therapy [7], and two with facial myokymia (FM) secondary to intracranial meningioma in one case [8] and inflammatory central nervous system (CNS) disease in the other [9].

The purpose of our retrospective case series was to report additional cases of naturally occurring focal myokymia and to describe the clinical presentation, diagnostic findings, treatment, and outcomes in dogs and cats with FM.

1.1 | Material and Methods

Medical records from six different referral institutions in the United Kingdom were reviewed to identify dogs and cats with clinically confirmed FM presented between 2006 and 2022. The study was approved by the Royal College of Veterinary Surgeons (RCVS) Ethics Review Panel.

Dogs and cats were included if a board-certified veterinary neurologist confirmed the presence of FM by observation of the characteristic clinical manifestation with or without electromyographic (EMG) confirmation of myokymic discharges in the muscles of facial expression. Patients were excluded if the FM was associated with or progressed to generalized myokymia, with or without neuromyotonia. Data collected included species, breed, age, sex, clinical presentation, results of ancillary diagnostic tests, final diagnosis, treatment, and outcome. In addition, all magnetic resonance imaging (MRI) studies (when performed) were retrospectively reviewed by a board-certified radiologist (CM). The radiologist was asked to evaluate whether the facial nerve and vestibulocochlear nerve were enlarged and contrast enhancing, whether the facial and vestibulocochlear nuclei and adjacent structures were affected, to classify the size of the caudal belly of the digastricus muscle as normal or having mild, moderate, or marked atrophy, and in cases that presented with signs of vestibular disease, to evaluate in detail whether any components of the central or peripheral vestibular system were affected. All MRIs were performed using a 1.5 Tesla magnet. Video footage showing FM was reviewed when available. Follow-up information was obtained from medical records, including re-examination appointments at the referral hospitals, and telephone updates were performed by the attending clinician when possible.

2 | Results

2.1 | Animals

Nine cases were identified; seven dogs and two cats. Dog breeds represented were Border terrier ($n = 2$), Yorkshire terrier ($n = 1$), Staffordshire bull terrier ($n = 1$), French bulldog ($n = 1$), Bichon frise ($n = 1$) and crossbreed ($n = 1$). Both cats were domestic shorthairs ($n = 2$). Four dogs were female (all spayed) and three were male (all neutered). Both cats were male and neutered. The median age for the dogs was 8.2 years (range, 6–12.1 years) whereas median age for the cats was 7.2 years (range, 4.9–9.3 years).

2.2 | Clinical History and Clinical Examination

The median duration of the neurological signs (other than FM) before consultation at the referral institutions was 31 days (range, 14–60 days). Facial myokymia was identified by the owner before referral in six cases (six dogs), and it was first noticed at the referral institutions in three cases (one dog and two cats). The median time that FM was visualized before consultation was 23 days (range, 0–60 days) and it was reported to be continuous in four and intermittent in two animals. Video footage of the FM was available in seven cases (five dogs and two cats); Video (S1).

A neurological examination was performed in all but one cat in which the FM was identified while the cat was under general anesthesia (GA). This cat was presented to the dentistry service 3 weeks after a ballistic orofacial trauma. Facial myokymia was unilateral in all cases, being right-sided in both cats, left-sided in five dogs, and right-sided in two dogs. Other cranial nerve deficits ipsilateral to the FM were identified in all cases in which a full neurologic examination was performed ($n = 8$). Concurrent ipsilateral vestibular signs were seen in six dogs and one cat ($n = 7$); ipsilateral head tilt was the most common vestibular sign (six dogs and one cat), followed by vestibular ataxia (two dogs) and ventrolateral positional strabismus (two dogs). Ipsilateral signs of facial nerve motor dysfunction other than FM were seen in three dogs, which included decreased menace response (Dogs 1 and 6) with normal bulbar retraction, decreased palpebral reflex (Dogs 5 and 6), absent palpebral reflex (Dog 1), and decreased tone of the ipsilateral muscles of facial expression (Dog 1).

Other neurological deficits were detected in three cases (two dogs and one cat). These included postural reaction deficits ipsilateral to the FM (Dogs 1 and 7), obtundation (Dog 1 and Cat 1), intermittent head turn and circling contralateral to the side of the FM (Dog 1), decreased nasal sensation ipsilateral to the FM (Dog 1), tongue atrophy ipsilateral to the FM (Dog 7), dysphonia (Dog 7), decreased jaw tone (Cat 1) and Horner syndrome ipsilateral to the FM (Cat 1) (Table S1).

Other clinical findings were discomfort when opening the mouth (Dog 6) or on cervical palpation (Dog 7) and intermittent face rubbing (Dog 4 and Cat 1).

The neurolocalization was left peripheral vestibular system and left facial nerve (Dogs 2 and 6), right peripheral vestibular system and right facial nerve (Dogs 3 and 4), left facial nerve (Dog 5), right facial nerve (Cat 2), left brainstem (Dog 7), right forebrain and left brainstem (Dog 1), and trigeminal nerve (motor) bilaterally, right facial nerve, right vestibulocochlear nerve, and sympathetic innervation of the right eye (Cat 1).

Previously diagnosed conditions included hyperadrenocorticism (Dog 5), idiopathic epilepsy (Dog 6) and mitral valve disease stage B2 (Dog 4). These patients were on treatment with trilostane, phenobarbitone, and pimobendan, respectively.

2.3 | Ancillary Diagnostic Tests

Ancillary diagnostic tests and results are present in Table S1.

2.4 | Magnetic Resonance Imaging Findings and Cerebrospinal Fluid Analysis

Magnetic resonance imaging was performed in eight cases (seven dogs and one cat); MRI details and facial nerve and nucleus MRI findings can be found in Table S2. Changes affecting the vestibulocochlear nerve and nucleus or facial nerve and nucleus are described below.

In dog 1, MRI showed multifocal intra-axial lesions with the largest lesion located in the left brainstem, medial to the internal acoustic meatus, in the region of the facial, vestibular, and trigeminal nuclei. Isolated ipsilateral changes in the facial and vestibulocochlear nerves, including thickening and contrast enhancement, were noted in dogs 2, 3 (Figure 1) and 4 (Figure 2). Mild involvement of the intracranial portion of these nerves also was noted in the initial MRI study of Dog 4. Follow-up MRI was available in Dogs 3 (Figure 1) and 4 (Figure 2), with no clinically relevant progression after 18 months in Dog 3 and clinically relevant progression on imaging (together with concurrent neurological deterioration) after 30 months in Dog 4, in which the intracranial portion of the facial and vestibulocochlear nerves had a strongly contrast enhancing mass-like appearance. In Dog 5, the intratemporal portions of the left facial and vestibulocochlear nerves were thickened and showed contrast enhancement. Moderate thickening and contrast enhancement of the left facial and vestibulocochlear nerves were present in Dog 6 (Figure 3). In Dog 7 (Figure 3), an extra-axial mass at the left cerebellopontine angle resulted in clinically relevant compression of the brainstem. Mild thickening and contrast enhancement of the left facial and vestibulocochlear nerves also was noted. Lastly, MRI in cat 1 showed suspected erosion of the skull base with

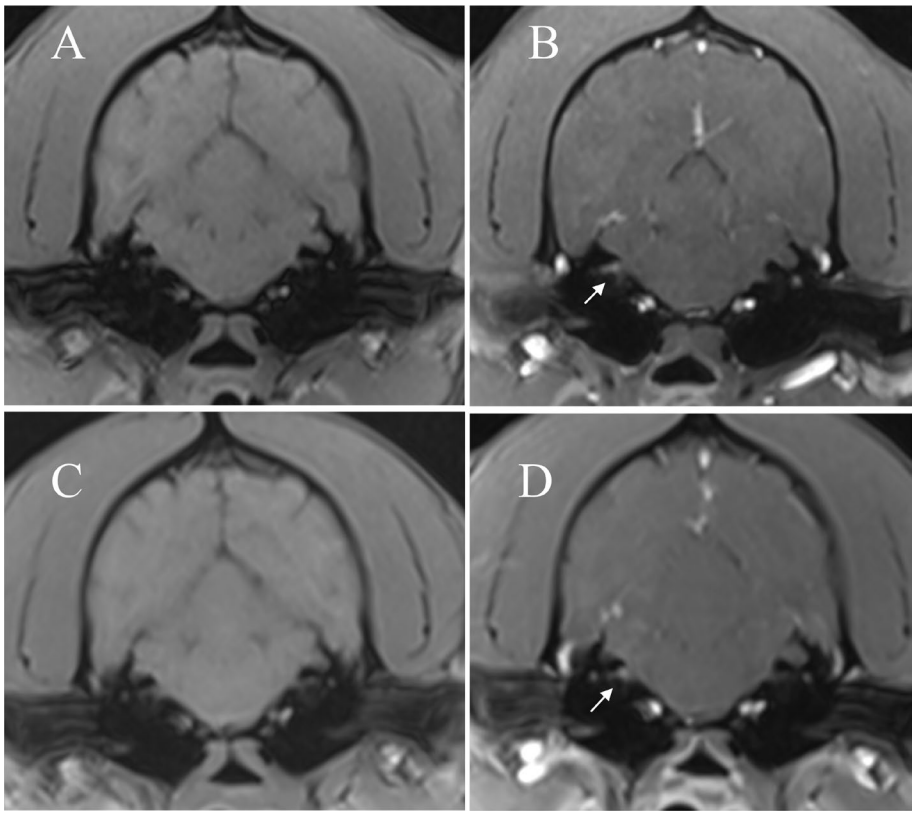

FIGURE 1 | Brain MRI (1.5 T magnet) at initial diagnosis (A, B) and follow-up MRI 18 months after diagnosis (C, D) of a dog with FVNUE (Dog 3). Transverse Fat saturation T1-weighted VIBE pre-contrast (A, C) and post-contrast (B, D) at the level of facial nerves (FN). Note the mildly thickened and contrast-enhancing right FN (arrows). No obvious progression of the previous findings or meningeal involvement were identified 18 months after diagnosis (D).

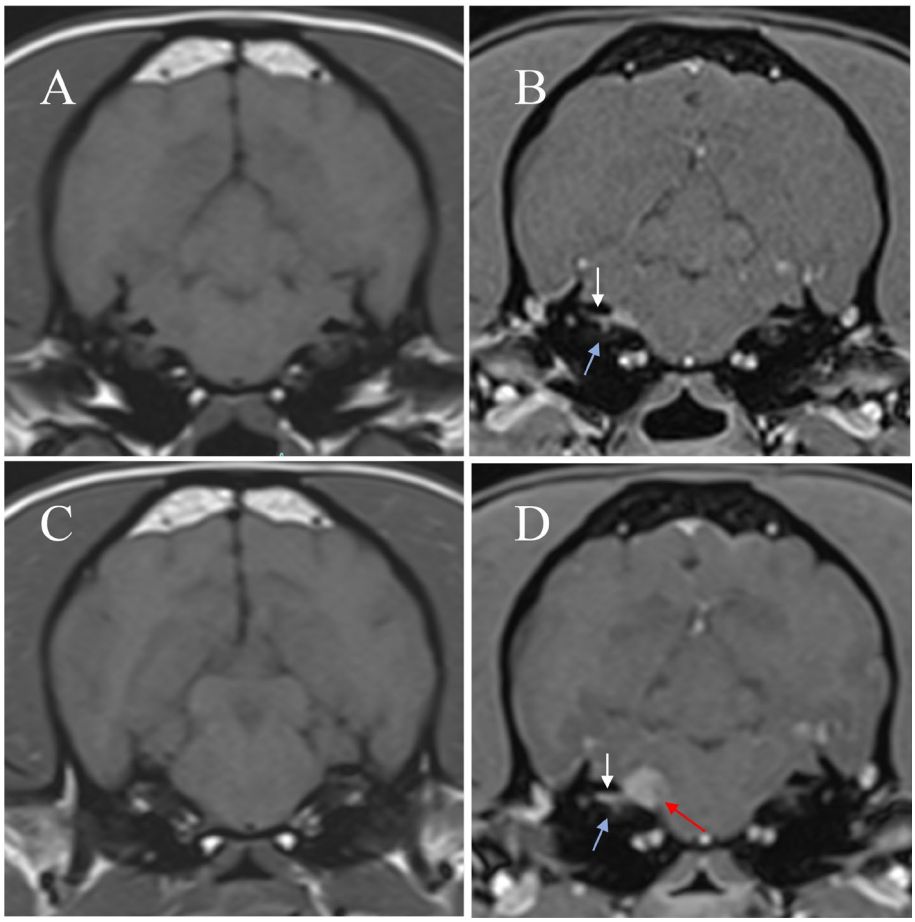

FIGURE 2 | Brain MRI (1.5 T magnet) at initial diagnosis (A, B) and follow-up MRI 30 months after diagnosis (C, D) of a dog diagnosed with a lesion compatible with neoplasia or hypertrophic neuritis (Dog 4). Transverse Fat saturation T1-weighted VIBE pre-contrast (A, C) and post-contrast (B, D) at the level of facial and vestibulocochlear nerves. Note the mildly thickened and contrast enhancing right facial (white arrow) and vestibulocochlear (blue arrow) nerves. In the follow-up MRI, there is significant progression of the previous findings, with a mass-like appearance of the intracranial portion of the previously thickened nerves (D, red arrow).

mild meningeal enhancement at the level of the right internal acoustic meatus.

Concurrent mild (Dogs 2,3 and 4 and Cat 1), moderate (Dogs 5,6 and 7) or marked (Dog 1) atrophy of the caudal belly of the digastric muscle, ipsilateral to the FM, was seen in all patients in which MRI was performed ($n = 8$). This feature was observed at the time of the first MRI in six dogs and one cat, and at follow-up MRI in Dog 3. The atrophy of the aforementioned muscle progressed from mild (first MRI) to marked (second MRI) in Dog 4.

Four dogs and one cat had cisternal cerebrospinal fluid analysis (CSF) sampling and analysis performed. Results were normal in all but one dog. Cerebrospinal fluid analysis in Dog 5 showed mild hemodilution (40 red blood cells/μL; reference, 0) with albuminocytologic dissociation (ACD; 61 mg/dL; reference, < 30). In dog 3, CSF PCR for infectious diseases (Bornavirus, *Borrelia burgdorferi*, *Ehrlichia/Anaplasma*, canine herpesvirus, *Leishmania*, *Neospora caninum*, canine parvovirus, *Toxoplasma gondii*, canine distemper virus and canine minute virus [carnivore bocaparvovirus-1; CBoV-1]) was positive for CBoV-1. Two dogs (Dogs 3 and 4) had repeat CSF collection at the time of follow-up MRI, and ACD was present in both cases (32 and 43 mg/dL, respectively; reference, < 30).

2.5 | Electromyography

Electromyography was performed in the visually affected superficial facial muscles in five cases (performed conscious in two dogs and under GA in two dogs and one cat). Electromyography confirmed the presence of myokymic discharges in all cases, and appeared as spontaneous bursts of motor unit action potentials firing at rates of 5 to 150 Hz. This motor unit activity was discontinuous and had variable patterns of discharge, including single discharges, doublets, triplets, and multiplets. Occasional fibrillation potentials and positive sharp waves also were recorded in one dog and one cat. In one dog and one cat, high-frequency (150–300 Hz) bursts of motor unit action potentials consistent with neuromyotonic discharges also were recorded. In two of the three patients undergoing EMG while anesthetized, myokymia was still visible at the time of testing, but myokymia was not visible after a longer period of anesthesia (Video S2; Figure 4).

2.6 | Diagnoses

The following diagnoses were made for the seven dogs: meningoencephalitis of unknown origin (MUO; Dog 1), facial and vestibular neuropathy of unknown etiology (FVNUE; Dogs 2

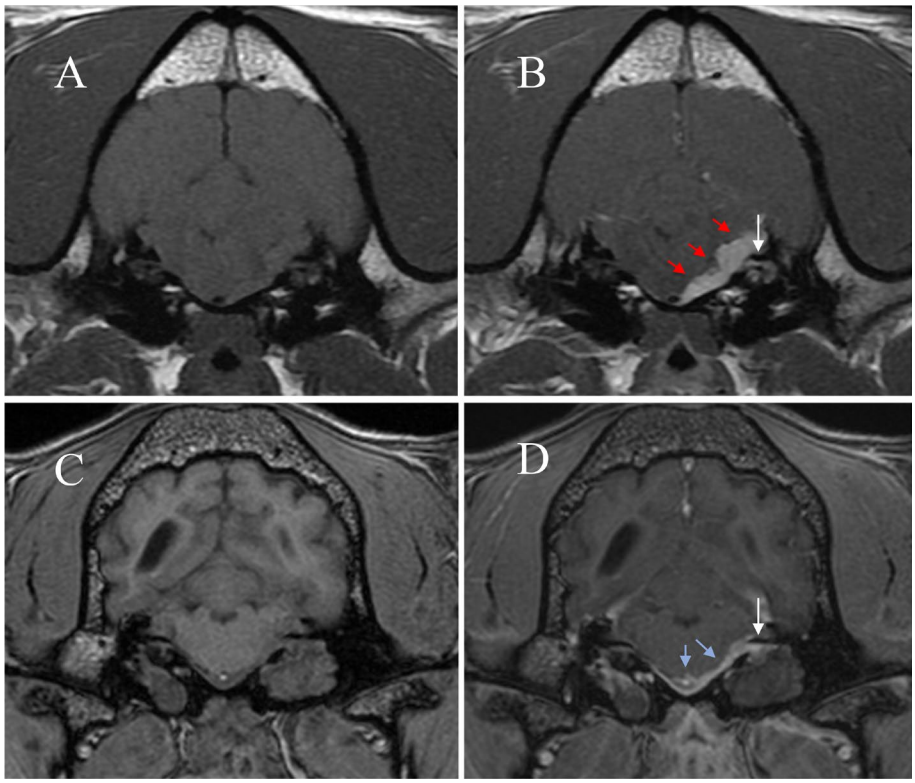

FIGURE 3 | Brain MRIs (1.5 T magnet) of a dog with a presumptive meningioma (A, B—dog 7) and a dog diagnosed with left sided otitis media-interna (C, D—dog 6). Transverse T1-weighted pre-contrast (A, C) and T1-weighted post contrast (B, D) at the level of the tympanic bullae. (A, B) note the plaque-like, broad-based and contrast enhancing extra axial lesion at the level of the left cerebellopontine angle (red arrows) and the mild thickening and contrast enhancement of the left facial nerve (white arrow). (C, D) Note the severe, expansile, left otitis media and interna with meningeal enhancement, intracranial extension (blue arrows) and left facial nerve thickening and contrast enhancement (white arrow).

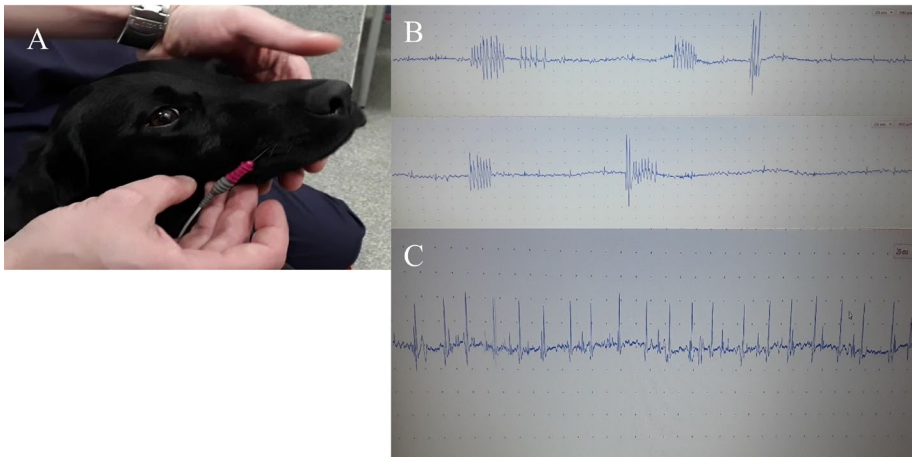

FIGURE 4 | (A) Recording spontaneous muscle activity in the levator nasolabialis muscle in an awake patient (dog 3). (B) Multiplets of spontaneous myofiber activity (myokymic discharges). (C) Neuromyotonic discharges with an intraburst frequency of 250 Hz.

and 3), left otitis interna, with associated facial and vestibulocochlear neuropathy, and a pituitary microadenoma (Dog 5), left otitis media and interna with intracranial extension (Dog 6), and a suspected meningioma (Dog 7). One dog initially was diagnosed with FVNUE (Dog 4), but a second MRI performed 30 months after the initial diagnosis showed progression of the previous findings, with the presence of a mass-like lesion considered more consistent with neoplasia (peripheral nerve sheath tumor, neurofibroma, lymphoma or meningioma) or, less likely, hypertrophic neuritis. For the two cats, the diagnoses were retrobulbar adenosquamous carcinoma (Cat 1) and orofacial trauma (Cat 2).

2.7 | Treatment and Outcome

Treatment was dependent on the etiologic diagnosis. The dog diagnosed with MUO (Dog 1) was started on an IV constant

rate infusion of cytarabine arabinoside (200 mg/m^2 over 12 h), immunosuppressive doses of prednisolone (2 mg/kg PO q24h), metronidazole (15 mg/kg PO q12h) for hemorrhagic diarrhea, and omeprazole (1 mg/kg PO q12h). A follow-up examination 3 weeks after discharge showed mild clinical improvement. Despite the persistence of left facial paresis (decreased palpebral reflex), the FM had completely resolved. The dog then deteriorated 4 weeks after diagnosis while the prednisolone was being tapered, with worsened vestibular ataxia, obtundation, left-sided facial paralysis, but no FM. The dog was euthanized at that time.

Both dogs with FVNUE were treated with prednisolone. Dog 2 received prednisolone at 0.75 mg/kg PO q12h, and the FM became less frequent and intense. The FM worsened when attempts were made to taper the prednisolone dose below 0.75 mg/kg PO q24h, and so this dose was maintained long term. Eighteen months after the initial presentation, the dog was re-evaluated at the referral hospital, and a mild residual left-sided head tilt was noted, but no FM. The dose of prednisolone was tapered over 2 months and subsequently stopped. No relapse of the FM was observed 22 months after diagnosis and 2 months after discontinuation of prednisolone. This dog was euthanized 28 months after diagnosis because of severe respiratory disease, with no FM reported at that time. The other dog diagnosed with FVNUE (Dog 3) responded to 0.5 mg/kg PO q12h of prednisolone, with almost complete resolution of the FM. Multiple attempts were made to taper the prednisolone dose further, but the myokymia recurred every time the prednisolone dose was decreased. An increase to an immunosuppressive dose (1 mg/kg PO q12h) was tried for 4 weeks, but the dog developed a severe corneal ulcer OD, and the eye was enucleated after decreasing the prednisolone dose. Subcutaneous cytarabine arabinose was administered for a total of 3 cycles (50 mg/m^2 q12h for four injections) at three-week intervals, but it was discontinued because of lack of response. Eighteen months after diagnosis, the dog was receiving prednisolone at 0.5 mg/kg q48h, and a follow-up MRI was performed. At this time, persistent right-sided head tilt and FM were present. After the MRI, the patient was treated with botulinum toxin type A (BoNT-A) injections (Botox), receiving a total of 150 units into the clinically affected muscles while under GA. Near-complete resolution of the myokymia was observed within 10 days after injections, but the myokymia slowly returned approximately 12 weeks later. Repeat Botox injections were declined by the owner. Treatment with mexiletine was tried for 2 months with a maximum dose of 6 mg/kg PO q8h; no improvement of the FM was seen, and treatment was stopped.

Dog 4, initially diagnosed with FVNUE, had complete resolution of the FM and improvement of the head tilt with prednisolone (1.2 mg/kg PO q24h). The dog then developed hemorrhagic diarrhea, and the dose of prednisolone was tapered and then stopped. Four weeks after discontinuing treatment with prednisolone, the FM recurred but subsequently resolved after prednisolone treatment was restarted (0.6 mg/kg PO q24h). However, the prednisolone was again discontinued because of adverse effects. The dog was reassessed 30 months after diagnosis because of neurological deterioration, with the owner reporting ongoing intermittent FM, right-sided head tilt, and development of right-sided facial paralysis. A repeat MRI identified progression of the imaging findings that prompted changing the presumptive diagnosis to neoplasia or hypertrophic neuritis; FM was seen at the time of the MRI. Analysis of CSF indicated ACD. Given the presence of concurrent heart disease and the reported adverse effects while previously receiving prednisolone, treatment was not restarted.

The dog diagnosed with otitis interna (Dog 5) was treated with amoxicillin/clavulanic acid (20 mg/kg PO q12h) for 2 weeks, along with meloxicam (0.1 mg/kg PO q24h) and gabapentin (13 mg/kg PO q8h), with complete resolution of the FM observed. Eight months after diagnosis, the FM recurred, and the dog also was reported to have become distressed and anxious; the dog was euthanized at that time without further investigations.

The dog with otitis media–interna with intracranial extension (Dog 6) underwent total ear canal ablation and lateral bulla osteotomy and was treated with clindamycin (12 mg/kg PO q12h for 7 weeks), gabapentin (10 mg/kg PO q12h) and paracetamol (15 mg/kg PO q12h). Two days after surgery, the FM had resolved. An update was obtained 6 weeks after discharge, and gradual clinical improvement was reported. The patient had started blinking again on the left side but mild vestibular ataxia and mild intermittent FM affecting the area of the left nostril and upper lip were reported. Four months after surgery, the dog developed discomfort when swallowing and neck muscle tremors, and the owner elected euthanasia; intermittent FM was still present at that time.

Dog 7 was diagnosed with a presumptive intracranial meningioma and treated with prednisolone (0.6 mg/kg PO q24h) and gabapentin (12 mg/kg PO q12h) and received radiotherapy (20 fractions × 2.5 Gray). Follow-up computed tomography performed 3 months after diagnosis showed a mild decrease in lesion size. The dog was reported to have improved clinically, and the FM had completely resolved. Six months after diagnosis, the dog had intermittent relapses of the FM, which resolved after increasing the dose of prednisolone. The dog was euthanized 12 months after diagnosis because of neurological deterioration (in the absence of FM) and suspected aspiration pneumonia.

The cat diagnosed with a retrobulbar adenosquamous cell carcinoma (Cat 1) was treated with prednisolone (1 mg/kg PO q24h) and gabapentin (10 mg/kg PO q8h). The FM improved, becoming less frequent and affecting only the caudal aspect of the ear, but subsequent clinical deterioration occurred, including blindness. Four weeks after diagnosis, the owner elected euthanasia. The cat with orofacial trauma after a ballistic injury (Cat 2) underwent multiple dental extractions. The cat was discharged on meloxicam for 10 days and was lost to follow-up.

3 | Discussion

Experimentally, FM has been induced in cats after the injection of kainic acid into the pons, adjacent to the facial nucleus [10]. However, clinical cases of FM have not been reported previously.

Facial myokymia is hypothesized to result from alterations in the microenvironment of the axonal membranes of the facial nerve, resulting in ectopic excitation at different sites between the facial nucleus and the motor unit [11]. It has been described in a variety of disorders in human medicine including multiple sclerosis (MS) [12], brainstem neoplasia [13], acoustic neurinoma

[14], Guillain-Barré syndrome [15], Bell's palsy [16], rattlesnake envenomation [17], in association with K^+ channel autoantibodies [18] and after radiotherapy [19]. Interestingly, voltage-gated potassium channel autoantibodies have been found in humans with pituitary adenoma and generalized myokymia, but the relationship between the autoantibodies and myokymic signs was not assessed [20]. One of the dogs described in our study was diagnosed with a pituitary mass. Given that the myokymia was focal and not generalized in this dog, the FM was thought to be related to thickening and contrast enhancement of the intratemporal portions of the left facial and vestibulocochlear nerves, resulting in secondary hyperexcitability of the facial nerve.

In our study, we describe FM appearing concomitantly or secondary to a wide variety of disorders, some of which have not been previously described in conjunction with FM in dogs and cats. One of the dogs in our study was diagnosed with FVNUE and tested positive for CBoV-1 (formerly canine minute virus or canine parvovirus type 1) by PCR on CSF. *Carnivore bocaparvovirus type-1* is a species of *Bocaparvovirus* of the family *Parvoviridae*. Clinical signs associated with CBoV-1 are primarily respiratory and gastrointestinal in young dogs [21]. *Carnivore bocaparvovirus type-1* also has been isolated from nine dogs with concurrent neurological disease: three were diagnosed with MUO, four with idiopathic epilepsy, and two were undiagnosed [22]. The clinical relevance of CBoV-1 in patients with neurological disease and its potential association with the FVNUE and FM observed in the dog in our study remain unknown.

The facial nerve accompanies the vestibulocochlear nerve into the internal acoustic meatus of the petrosal portion of the temporal bone and then enters the facial canal within the temporal bone, emerging through the stylomastoid foramen. Branches of the facial nerve are distributed to the muscles of facial expression, which are relatively thin muscles of the ear, eyelids, nose, cheeks, and lips [23]. In our study, MRI abnormalities affecting either the facial motor nucleus or facial nerve were detected in all eight cases in which this imaging modality was performed. Differentiating the affected intratemporal portions of the facial nerve was attempted, but not all cases had thin slice sequences, and therefore not all intratemporal portions could be reliably visualized and assessed [24].

In the two dogs in which FNVUE was diagnosed, changes affecting the facial and vestibulocochlear nerves were detected, but the cause of these changes was unknown in the absence of histopathology. Similar changes, also affecting the intracranial portions of the nerves, were identified in another dog, but follow-up MRI performed 30 months after the initial presentation showed progression of the previous findings and identified a mass-like lesion of the intracranial portion of the facial and vestibulocochlear nerves. No definitive diagnosis was achieved in this case, but a neoplastic or hypertrophic inflammatory process was suspected given the progression of the imaging findings. In the dog with otitis interna, the facial nerve thickening and contrast enhancement may have been secondary to vestibulocochlear nerve involvement. Direct irritation of the facial nerve or facial nucleus or indirect mass effect with neurovascular compression, was suspected to be the cause of the FM in the remaining dogs and cats in our study.

The facial nerve provides motor function to the muscles of facial expression and to the caudal portion of the digastric muscle [23]. Ipsilateral atrophy of the caudal belly of the digastric muscle occurs in approximately 90% of dogs with idiopathic facial neuropathy [25]. We identified different degrees of atrophy of the caudal portion of the digastric muscle ipsilateral to the FM in all patients that underwent MRI ($n=8$), supporting the presence of some degree of axonal loss in the motor portion of the facial nerve, despite the fact that motor nerve dysfunction (i.e., facial paresis or paralysis) was not detected on neurological examination in five of these cases. In these four dogs and one cat, FM was the only clinical manifestation of facial nerve dysfunction. However, the presence of fibrillation potentials and positive sharp waves on EMG of the visibly affected superficial facial muscles in one dog and one cat (two of the five animals in which EMG was performed) further supports the presence of axonal loss in these animals.

The majority of patients in our study (six dogs and one cat) had concurrent vestibular signs, likely explained by the close anatomical relationship between the facial and vestibulocochlear nerves. This conclusion is supported by the fact that changes affecting the vestibulocochlear nerve ($n=4$), vestibular nuclei ($n=2$) and meninges at the level of the internal acoustic meatus ($n=1$) were observed on MRI in these cases. Interestingly, in the patient diagnosed with otitis interna (dog 5), no vestibular signs were identified upon examination, despite MRI changes affecting the inner ear, together with thickening and contrast enhancement of the vestibulocochlear nerve; the reason for this discrepancy is unknown. The cat with orofacial trauma had no involvement of the vestibular system, and the FM in this case was most likely secondary to direct damage to the superficial branches of the facial nerve distal to the stylomastoid foramen, in proximity to the mandibular and maxillary trauma caused by the bullet injury.

Treatment of peripheral nerve hyperexcitability (PNH) in dogs and cats with generalized myokymia and neuromyotonia has been based on treatments used in humans, which include avoidance of stress factors and the use of sodium channel blockers, such as phenytoin, carbamazepine, mexiletine, or procainamide [26, 27]. The clinical efficacy of these membrane-stabilizing agents is typically only temporary in dogs, with the reappearance of signs of PNH several months after the start of treatment [27]. Membrane-stabilizing drugs (mexiletine) were only used in one dog in our study, and thus conclusions on their efficacy for the treatment of FM cannot be made. Limited information is available about the treatment of FM in veterinary medicine. Prednisolone was trialed unsuccessfully in a puppy with presumptive CNS inflammation [9] and a 7-day course of enrofloxacin followed by a 7-day course of prednisolone also was used unsuccessfully to treat FM secondary to a suspected meningioma involving the internal acoustic meatus in another case [8]. In a dog with focal palatolingual myokymia, treatment with slow-release phenytoin was trialed and was unsuccessful [6]. Corticosteroids have been used in human patients with FM secondary to MS, with the majority of cases showing improvement [12]. However, the impact of corticosteroids on the clinical course is unclear because both the treated (corticosteroids, carbamazepine, gabapentin, baclofen) and untreated groups had resolution of the FM within months of initial presentation, suggesting that FM in MS might be a self-limiting process. Whether

the efficacy of prednisolone for control of FM is a result of a direct effect on the excitability of the facial nerve by decreasing edema and inflammation, or secondary to the management of the underlying disease process is likely to depend on the cause and remains to be determined. In our study, prednisolone was used to treat the underlying disease process in three cases (Dogs 1 and 7 and Cat 1) and it was used to specifically treat the FM in three cases in which FVNUE was suspected (Dogs 2, 3 and 4). In the latter, prednisolone was used because MRI changes were seen in both the facial and vestibulocochlear nerves. In veterinary medicine, it is currently unknown whether dogs and cats with facial or vestibulocochlear neuropathy benefit or not from treatment with corticosteroids. High-dose PO corticosteroids commenced within 72 h of onset improve outcomes in humans with Bell's palsy, as proven in randomized controlled trials [28, 29]. Similar studies are difficult to perform in dogs because patients frequently are not seen within the first 72 h, and a large number of affected dogs will be needed to achieve statistical significance. When prednisolone was used (either alone or in combination with other treatments), FM improved or resolved, but relapses were common.

Botulinum neurotoxin type A has been used successfully in humans to treat a variety of focal dystonias, occasionally in orbicularis myokymia, and also in continuous hemifacial myokymia secondary to MS [30]. It also has been used successfully in a dog to treat focal myokymia and neuromyotonia affecting a limb after radiation [7]. In our study, we report its use for the treatment of FM in one dog diagnosed with FVNUE. The FM in this case showed near complete resolution after Botox injection but recurred after 12 weeks. Additional injections and dose adjustments in an attempt to achieve full and persistent resolution were proposed but declined by the owner. Botulinum neurotoxin type A interferes with neural transmission by blocking the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction, and causing muscle paralysis. The relaxation induced by injection with BoNT-A usually lasts approximately three months [31], as supported by the case in our study.

In one study evaluating 43 human patients with FM of different causes, FM was identified by the patients themselves less than half of the time (20/43) [32]. Some of these patients noticed the FM because of a subjective abnormal sensation, whereas others identified it by looking in the mirror. Occasionally, myokymia was only identified on EMG (4/43) [32]. Only two patients in our study (Dog 4 and Cat 1) showed intermittent face rubbing as a possible sign of facial pain or irritation related to FM. In Cat 1, the retrobulbar mass and suspected involvement of the trigeminal nerve could have been responsible for facial discomfort, but no abnormal facial sensation was detected clinically in this case. In humans with FM, abnormal sensations such as numbness have been reported [30], but pain is not a common complaint. Furthermore, treatment seems to focus on the management of the FM rather than alleviation of pain per se. Because veterinary patients are unable to verbalize symptoms of pain, additional studies involving more objective assessments of discomfort are required to determine whether FM may be a cause of facial pain in dogs and cats.

Detrimental effects on quality of life because of FM were not apparent in our retrospective study, but such effects warrant further evaluation in future studies. Improvement or resolution of the FM did not appear to affect overall outcome. Therefore, the need for primary treatment of FM in veterinary medicine is likely to be on a case-by-case basis, and treatment should focus on addressing the underlying cause.

Myokymia and neuromyotonia may persist under GA clinically and electrophysiologically in dogs and cats [5, 33]. In humans, excessive motor unit activity of peripheral nerve origin is not substantially altered by sleep or GA [34]. Limited information on focal myokymia under GA is available in human patients because anesthesia is not usually required to perform EMG in humans. In our study, myokymia was no longer visible in two dogs while anesthetized, but only after prolonged GA. In Cat 1, FM was first identified under GA.

Our study had limitations, mainly related to its retrospective and multicenter nature. Although myokymia is a distinctive clinical feature, not all the patients had EMG to confirm the presence of myokymic discharges. Another important limitation is the lack of a histopathological diagnosis in most cases, which was only available for one dog and one cat. Furthermore, the histopathological examinations did not evaluate all possible anatomical structures that could have caused the FM. However, examining the facial nerve after it emerges from the brainstem and travels along the facial canal poses challenges because of the difficulty in sample collection and the need for decalcifying techniques. Patients with FVNUE in our study could have been misdiagnosed; repeat imaging may not have been sufficiently delayed to observe pathological changes on MRI in one dog (Dog 3) and follow-up MRI was not performed in the other dog (Dog 2). However, in the dog that lacked a repeat MRI, the FM resolved, and 22 months after diagnosis other clinical signs were absent (other than mild persistent residual head tilt), making a neoplastic process less likely.

In conclusion, we have described the clinical presentation, different underlying pathologic lesions, treatment, and outcome in nine animals with FM. Facial myokymia can be caused by a range of underlying disorders, with structural involvement of the facial nucleus or nerve being common. In all of the patients that underwent MRI of the head in our study, an abnormality was identified to explain the observed FM. These included several causes of FM not previously reported in the veterinary literature: two dogs with FVNUE, two with otitis (one with otitis media-interna and one with otitis interna alone) and one cat with orofacial trauma. Treatment and final outcome depend on the underlying cause, but improvement or resolution of FM is possible.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Approved by the clinical ethical research committee board of the Royal College of Veterinary Surgeons (reference number 2016 1526B). Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.