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CASE REPORT

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Saccadic oscillations in 4 dogs and 1 cat

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Disorders affecting the control of saccadic eye movements result in involuntary saccadic oscillations and are widely reported in human medicine. Information regarding the occurrence and potential importance of saccadic oscillations in veterinary medicine is currently limited. The clinical histories of three dogs and one cat displaying involuntary eye movements consistent with opsoclonus are presented, with final diagnoses including idiopathic generalized tremor syndrome and neuronal ceroid lipofuscinosis (NCL). A dog with eye movements closely resembling macrosaccadic oscillations is also presented, for which a final diagnosis of NCL was made. All animals had clinical signs of cerebellar disease. As in human medicine, recognition of these forms of involuntary eye movement might suggest a cerebellar neuroanatomic localization. Opsoclonus and macrosaccadic oscillations are forms of involuntary saccadic eye movement that are both unrecognized and under-reported in veterinary medicine.

KEYWORDS
cerebellum, macrosaccadic oscillations, opsoclonus, vestibular disease

1 | INTRODUCTION

The control of eyeball position and movement is complex and involves numerous interconnected neural structures and pathways. The vestibular system, and its connections to the muscles for eye movement, is responsible for maintaining the position of the eyes relative to the position and movement of the head.[1-3] A large number of pathways also exist for the initiation and control of saccadic eye movements, which are required to voluntarily move gaze from one target of interest to another. These gaze fixing and gaze shifting mechanisms allow for accurate focusing on objects within the visual field.[4] Interruption to the normal functioning of these pathways can result in involuntary eye movements, observed clinically as inappropriate, to-and-fro oscillations of the eyeballs. Disorders affecting the control of eye movements by the vestibular system result in a form of spontaneous eye movement called a jerk nystagmus.[1-3] These oscillations, which can be horizontal, vertical or rotatory/torsional, are characterized by a smooth, drifting eye movement followed by a fast corrective phase. In contrast, disorders affecting the control of saccadic eye movements result in forms of saccadic oscillations that are initiated by a fast, saccadic eye movement rather than having an initial slow drift phase.[4,5]

While there are numerous publications in human medicine focusing on the description, classification and pathophysiology underlying different forms of involuntary eye movement, information regarding the occurrence and potential importance of movements other than nystagmus is currently limited in veterinary medicine. The aim of our article is to raise awareness of other forms of involuntary eye movement that can be observed in dogs and cats. The clinical histories of four dogs and one cat presenting with eye movements that appeared consistent with forms of saccadic oscillations described in human medicine are reported, and the potential relevance of these different eye movements in veterinary medicine is discussed.

1.1 | Case 1

A 1-year, 7-month-old male neutered Cocker Spaniel-Poodle cross breed dog presented with a 4-day history of ataxia and generalized tremors. Bilateral, mild otitis externa was the only abnormality detected on general physical examination. Neurological examination revealed an alert mentation, ataxia of all limbs with a cerebellovestibular nature, falling to the right side, delayed and dysmetric hopping in the right thoracic and pelvic limbs, and severe generalized tremors of the whole

Abbreviations: CSF, cerebrospinal fluid; FIP, feline infectious peritonitis; MRI, magnetic resonance imaging; NCL, neuronal ceroid lipofuscinosis.

body that worsened with excitement or handling. Proprioceptive positioning was normal in all limbs. Cranial nerve examination revealed a right head tilt, positional ventrolateral strabismus in the right eye on head elevation, and rapid, conjugate, spontaneous eye movements, without a drift phase, occurring randomly in all directions (Supporting Information Video S1). These eye movements were considered to be most consistent with those defined as opsoclonus in human medicine.[4-6] The neuroanatomic localization was a diffuse encephalopathy, particularly affecting the cerebellovestibular system. Abnormalities were not detected on hematology and serum biochemistry. Serum *Neospora caninum* antibody testing was negative at 1 : 50 dilution. Magnetic resonance imaging (MRI) of the brain (Achieva 1.5T, Philips Medical Systems, Best, the Netherlands) did not reveal abnormalities. Cerebrospinal fluid (CSF) collected from the cisterna magna had an elevated total protein 43 mg/dL (reference <30 mg/dL) and a mild mononuclear pleocytosis of 15 cells/μL (reference <5 cells/μL). These findings, together with the signalment, history, and clinical signs, were most consistent with a diagnosis of idiopathic generalized tremor syndrome. Treatment consisted of administration of prednisolone (1 mg/kg PO q12h; Prednicare 5 mg tablets, Animalcare, York, UK) and cytosine arabinoside (50 mg/m^2 by SC injection twice daily for 4 doses; Cytarabine 20 mg/mL, Hospira UK, Hurley, UK). Reassessment two weeks after starting treatment revealed resolution of the spontaneous eye movements and marked improvement in both gait and the severity of tremors. The prednisolone dose was tapered to 0.5 mg/kg every third day over a 6-month period. The dog showed a relapse of generalized tremors at this time, which showed subsequent resolution after reintroduction of prednisolone (1 mg/kg PO q12h). The prednisolone dose was gradually tapered to 0.5 mg/kg every third day and the dog was reported to be normal by his owners at telephone follow-up 15 months after initial presentation.

1.2 | Case 2

A 5-year-old female neutered English springer spaniel presented with a 3-week history of acute, nonprogressive lethargy, nervousness, and apparent visual impairment. Her owners reported that she had become reluctant to jump into and out of the car and that she appeared to have difficulty judging distances or heights. Vision at other times was reported to be normal. General physical examination did not reveal abnormalities. Neurological examination revealed a mild right head tilt, mild ataxia of all limbs with a vestibular nature (drifting to the right), intermittent, involuntary contractions of the muscles of the ears, lips, and eyelids (facial myoclonus), and rapid, conjugate, spontaneous eye movements of variable amplitude occurring randomly in all directions, consistent with opsoclonus. Proprioception and segmental spinal reflexes were normal in all limbs. Abnormalities were not detected on hematology, serum biochemistry, thoracic radiography, abdominal ultrasonography, brain MRI (VetMR Grande 0.25T, Esaote, Genova, Italy) and analysis of CSF collected from the cisterna magna. In light of the normal diagnostic investigation results and static clinical signs, her owners opted to monitor her progress without treatment. The clinical signs remained static for 4 weeks before showing a complete, spontaneous resolution. No relapse or other medical problems were reported at telephone follow-up one year after initial presentation.

1.3 | Case 3

A 6-year-old female American Staffordshire Terrier presented with a chronic, progressive history of balance loss. Her owners reported that quick changes in direction, head shaking, or attempts to descend stairs would result in falls. On evaluation, she was bright, alert, and responsive but with ataxia of all limbs that had both a vestibular (veering off a straight line in both directions) and a cerebellar quality (hypermetria). Cranial nerve examination revealed inconsistent menace responses in both eyes, with apparently normal vision in that she could still track objects. Small head movements elicited rapid, low amplitude, multidirectional eye movements without a drift phase, consistent with opsoclonus. She had a fine intention tremor involving the head, truncal sway, and good motor strength. Proprioceptive positioning was normal but hopping was delayed in all limbs. A neuroanatomic diagnosis of a diffuse cerebellovestibular lesion was made. Hematology and serum biochemistry did not reveal abnormalities. Brain MRI (Symphony 1.5T, Siemens, Cary, North Carolina) revealed atrophy of the cerebellum, with a brainstem to cerebellum mid-sagittal cross-sectional area ratio of 114.8% (reference range 56.8%–85.2%).[7] Cerebrospinal fluid analysis was not performed at the owner's request. Infectious disease testing was not performed given the chronicity of the clinical signs and the occurrence of cerebellar degeneration in several generations of closely related dogs. Genetic testing subsequently confirmed the presence of a mutation in the arylsulfatase G gene and a diagnosis of neuronal ceroid lipofuscinosis (NCL) was made, which was confirmed at necropsy 4 years later.[8]

1.4 | Case 4

An 11-month-old male neutered Dachshund presented with a 3-month history of progressive balance loss. The dog was the result of a consanguineous mating between mother and son and was the only survivor of a litter of 4 puppies. Abnormalities were not detected on general physical examination. Neurological examination revealed profound vestibular ataxia with a tendency to fall and roll to the right, mildly delayed proprioceptive positioning in all limbs, markedly reduced to absent hopping in all limbs, and no extensor postural thrust. Occasional attempts to hop had a hypermetric quality to them. Throughout the examination, he had intermittent myoclonic jerks of the head, and he constantly licked and swallowed. Cranial nerve examination revealed absent menace responses bilaterally with intact pupillary light reflexes, and left-sided facial hypalgesia. The most dramatic finding on examination was the presence of rapid eye movements, triggered by a shift in gaze, which were wide at first and showed a gradual reduction in amplitude, moving around the mid-point he was attempting to fixate on (Supporting Information Video S2). These eye movements were predominantly horizontal in nature but could also become vertical, and were interpreted as being most consistent with those defined as macrosaccadic oscillations in human medicine.[4,5] Vision could not be assessed separately as the dog could not walk to negotiate an obstacle course and

the spontaneous eye movements complicated the interpretation of visual tracking. Hematology, serum biochemistry, and urinalysis did not reveal abnormalities. MRI of the brain (Symphony 1.5T, Siemens, Cary, North Carolina) revealed diffuse atrophy of the cerebellum and cerebrum with bilateral subdural hematomas, worse on the right side, identified as subdural T2W hyperintense material that did not suppress on FLAIR sequences, suggesting high protein or cellular content, coupled with gravity dependent T2W isointense material that had a susceptibility artifact on gradient echo T2* sequences. The dog was humanely euthanized and submitted for necropsy. A diagnosis of juvenile NCL was made and confirmed with genetic testing.

1.5 | Case 5

A 5-month-old male neutered domestic short hair cat presented with a 2-week history of severe generalized tremors. The cat appeared normal at rest, with an alert and appropriate mentation, but was reluctant to walk. When initiating movement, the cat developed a dramatic action-related tremor that worsened with intention. The cat appeared mildly ataxic when walking, although the intensity of tremors made gait evaluation difficult. Mild deficits in hopping and extensor postural thrust were noted in all limbs. Cranial nerve evaluation was unremarkable other than rapid, multidirectional eye movements initiated by a shift in gaze, most consistent with opsoclonus (Supporting Information Video S3). These clinical signs were suggestive of a diffuse encephalomyelopathy, with a predominance of cerebellovestibular signs. Routine hematology, serum biochemistry, and preprandial and postprandial bile acid testing did not reveal abnormalities. Serologic testing for feline leukemia virus, feline immunodeficiency virus, and *Toxoplasma gondii* was negative. Feline infectious peritonitis (FIP) was considered as an important differential diagnosis in a young cat with clinical signs of encephalopathy; however, it was considered less likely given the diffuse rather than focal or multifocal neuroanatomic localization. Further diagnostics were declined by the owners and the cat was started on prednisolone (Qualitest prednisolone oral solution USP [15 mg/5 mL], Huntsville, Alabama) for possible idiopathic generalized tremor syndrome (1 mg/kg PO q12h for 1 month, then q24h until follow-up).[9] The cat was clinically normal at recheck examination, and the prednisolone dose was gradually tapered over the next 2 months, without a recurrence of clinical signs. This complete resolution of clinical signs without relapse was considered inconsistent with that reported for cats with FIP.

2 | DISCUSSION

The neural control of eye movements is complex and despite intensive research in human medicine over greater than three decades, the precise pathways and mechanisms of control are still incompletely understood.[4] Both naturally occurring and experimental lesions to the numerous structures involved in the control of eye movements can result in abnormal, involuntary eyeball oscillations. These are commonly encountered in veterinary practice in the form of a spontaneous jerk nystagmus secondary to disorders affecting the central or peripheral components of the vestibular system.[1-3] As such, recognition of abnormal nystagmus on neurological examination raises strong suspicion of a lesion affecting the vestibular system, thus guiding the neurolocalization, differential diagnoses, and choice of further investigations.[1,2,10]

Disorders affecting the control of saccadic eye movements present as spontaneous, rapid, saccadic oscillations, without the initial drift phase that distinguishes them from jerk nystagmus.[4-6,11] Such disorders are widely recognized in human medicine, with classification dependent on the waveform and nature of the spontaneous eye movements. Differentiating between these forms of involuntary eye movement is important, as certain movements might be highly suggestive for a specific neuroanatomical localization or a certain disease process. Only anecdotal reports with inconsistent terminology have been used to describe naturally occurring saccadic oscillations in veterinary medicine until a recent case series describing convergence-retraction nystagmus in 3 dogs with lesions in the dorsal midbrain.[12] The alternative term convergence-retraction pulses has been suggested in human medicine to differentiate this form of saccadic oscillation from a true nystagmus.[5]

Other forms of saccadic oscillations described in human medicine include opsoclonus and macrosaccadic oscillations. Opsoclonus is characterized by bursts of rapid, multidirectional (horizontal, vertical, and rotatory) eye movements without an interval between saccades.[4-6,11] If these movements are restricted to the horizontal plane then they are termed ocular flutter.[4,6] The term "opsoclonus" is used in one veterinary textbook to describe "rapid abnormal eye movements" seen as an adverse effect of propofol administration,[13,14] and in another textbook as "a form of rapid pendular nystagmus in which the excursions of each eye are of equal speed and distance" seen in association with idiopathic generalized tremor syndrome in dogs.[1] While the latter description appears similar to ocular flutter in human medicine, neither describe the chaotic, multidirectional nature of true opsoclonus.[4-6,11] Rapid multidirectional eye movements have been described anecdotally in dogs with idiopathic generalized tremor syndrome, consistent with those observed in Cases 1 and 5 of this report.[14] The most common etiologies underlying opsoclonus in human patients are parainfectious (eg, viral) encephalitis, with presumed cerebellar involvement, or as a paraneoplastic syndrome secondary to distant tumors of the lung, breast or ovary in adults, and neuroblastoma in children.[6,11] Idiopathic generalized tremor syndrome is a presumed sterile inflammatory central nervous system disease[1,15]; therefore, the observation of opsoclonus in these cases might be analogous to that described secondary to certain forms of encephalitis in humans. Idiopathic opsoclonus occurs in humans and is associated with a spontaneous remission and good prognosis in the majority of patients.[6] This might be similar to the presentation and clinical course observed in Case 2 of this case series. The mechanisms underlying opsoclonus in humans remain incompletely understood, but histopathological examination and functional MRI currently support disinhibition (ie, activation) of the fastigial nuclei in the cerebellum secondary to dysfunction of the Purkinje cells in the dorsal vermis.[4,6,11,16,17] Recognition of opsoclonus in the American Staffordshire Terrier presented in Case 3, that was diagnosed with NCL and cerebellar cortical degeneration, could add support to a similar association between recognition of this form of eye movement and a cerebellar neurolocalization in veterinary medicine.

Macrosaccadic oscillations consist of runs of horizontal saccades that are induced when shifting gaze. These abnormal saccadic movements spontaneously build up and then decrease in amplitude, oscillate around a fixation point and are separated by a normal intersaccadic interval of ~200 ms.[4] To the author's knowledge, this distinctive form of eye movement has not been previously reported in veterinary medicine. The term "saccadic dysmetria" has been used to describe the ocular motor abnormalities observed in young Coton de Tulear dogs with neonatal cerebellar ataxia.[18] However, a further description of these eye movements is not provided to enable comparison to those described in human medicine. Macrosaccadic oscillations are most frequently observed in human patients with destructive lesions affecting the cerebellar nuclei,[2] but they have also been described in association with hereditary cerebellar ataxias[19] and rarely after lesions to certain pontine structures.[20,21] The Dachshund with suspected macrosaccadic oscillations in our study (Case 4) was diagnosed with NCL and had both clinical signs and MRI changes consistent with cerebellar disease. Given the association between this type of eye movement and cerebellar disease in humans, we suspect the Dachshund's ocular signs resulted from cerebellar degeneration, but lesions involving the retina or other regions of the brain affected by NCL could have also been responsible.

While the cases described in our study presented with striking involuntary eye movements that appeared consistent with those described as opsoclonus and macrosaccadic oscillations in human medicine, some caution must be applied in this interpretation. In-depth analysis of involuntary eye movements in human medicine relies upon complex electrophysiological testing to track and record these movements, such as electronystagmography or electrooculography.[22] These tests were not used to definitively characterize the eye movements observed in the cases described in our study, and would be required to analyze precise factors such as the presence or absence of an intersaccadic interval lasting ~200 ms in the case of macrosaccadic oscillations. Availability of such equipment and practical considerations regarding its use in awake animals may complicate the definitive classification of involuntary eye movements in veterinary medicine and limit direct comparison to analogous conditions in humans. It should also be considered that the neural structures responsible for control of eye movements in veterinary species are likely be both anatomically and physiologically different to those in human patients. Further work is therefore required to characterize different forms of saccadic oscillations in veterinary medicine and to determine their potential relevance in terms of neurolocalization, as for human patients.

Opsoclonus and macrosaccadic oscillations are forms of involuntary eye movement that have not previously been reported in cats or dogs. Clinical recognition of different types of saccadic oscillations might be of use in refining the neurolocalization, upon which a list of differential diagnoses can be formed to guide further investigations. It is likely that involuntary eye movements other than nystagmus are both unrecognized and under-reported in veterinary medicine.

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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.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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