Tremor syndromes in dogs and cats: an update

Tremor syndromes in dogs and cats might include tremors and twitches. Tremors are movement disorders that resemble involuntary rhythmic oscillatory sinusoidal movements of a body part. Twitches are caused by peripheral nerve hyperexcitability and they have variable frequency and amplitude. When twitches are manifested as generalised fasciculations they can mimic tremors. Tremors and twitches are common presenting complaints of dogs and cats in daily veterinary practice, and the clinician should be aware of them and their most common underlying aetiologies. Thorough tremor and twitch assessment is imperative to help the clinician come to a more specific conclusion regarding the nature and origin of these clinical signs. History, occurrence, localisation, direction, distractibility, intentionality, observation of tremor during stances, weight-bearing lifting test, auscultation and palpation of the trembling part and conscious electromyography are important parts of a thorough clinical assessment of tremors and twitches. Further studies are necessary to better characterise yet unknown tremor syndromes in dogs and cats.

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Theofanis Liatis DVM MRCVS ECVN Resident in Veterinary Neurology and Neurosurgery; **Steven De Decker** DVM MVetMed PhD FHEA MRCVS Professor in Veterinary Neurology and Neurosurgery; Royal Veterinary College, University of London, Hatfield, UK; Email: theofanis.liatis@gmail.com

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Tremor syndromes are movement disorders that have been rarely investigated in veterinary neurology of dogs and cats. Tremors are involuntary, rhythmic oscillatory movements of a body part with symmetric velocity in both directions of movement (such as sinusoidal movements) around a joint axis (Cerda-Gonzalez et al, 2021). Tremors can be classified by their age of onset, distribution, frequency of occurrence, activating conditions and frequency (Hz) (Cerda-Gonzalez et al, 2021).

Classification of tremors based on activation pattern has been adopted from human neurology and recently applied in veterinary medicine (Lowrie and Garosi, 2016a; Cerda-Gonzalez et al, 2021):

1. Resting tremor: a tremor of a part of the body that is not actively supported against gravity (for example, in a recumbent position) and is not voluntarily activated (not yet reported in veterinary medicine)
2. Action tremor: a tremor of a part of the body which is supported against gravity or makes a movement
   a. Postural tremor: tremor of a part of the body which is supported against gravity which usually ceases on activity or upon lying down (for example, senile tremor, orthostatic tremor or episodic non-intentional head tremor)
   b. Kinetic tremor: tremor of a part of the body occurring during any aspect of voluntary movement. It can be present when the movement begins, during the course of movement and as the target is reached (for example, an intention tremor); it typically originates from the cerebellum.

Twitches caused by peripheral nerve hyperexcitability can mimic tremors (Lowrie and Garosi, 2016a; Cerda-Gonzalez et al, 2021).

Action-related postural tremors

Orthostatic tremor

Orthostatic tremor is a rare tremor that predominantly affects the limbs, exclusively while standing with pathognomonic high-frequency muscle discharges (>12 Hz) on conscious electromyography (Liatis et al, 2022a). Its pathophysiology is unknown, but a central oscillator, located in the brainstem in the cerebellum, has been hypothesised to generate orthostatic tremors and it is considered a neurodegenerative disease (Benito-Leon and Domingo-Santos, 2016; Schoberl et al, 2017). It was first reported in Great Danes (Garosi et al, 2005) and it is a disease of purebred giant or large breed dogs that usually occurs over 4 months of age or between 9 months and 2 years old (Liatis et al, 2022a). In 62% of dogs, tremors can progress in intensity or expand to the thoracic limbs, trunk and head and a genetic predisposition has been suspected (Liatis et al, 2022a).

Orthostatic tremor is usually primary when it is manifested as a sole sign. When it is concomitant with other neurological, electrophysiological or imaging findings, it is classified as orthostatic tremor-plus. When the underlying disease in orthostatic tremor-plus is the cause of the tremor, then the orthostatic tremor can be considered symptomatic (Liatis et al, 2022a).

The semiology of primary orthostatic tremors includes tremors usually affecting the pelvic limbs (*Video 1*); in some dogs with high frequency tremors, the tremors might be more palpable than visible, and these dogs can present with a 'dancing sign' which is characterised by alternating weight from one limb to another in an attempt to avoid the disturbing tremors. Additional signs include difficulty sitting or rising, wide-based stance, wide-based gait on tandem walk, difficulty maintaining posture during specific activities (like eating) and, in severe cases, tendency to fall (postural instability) (Liatis et al, 2022a).

Diagnostically, a 'helicopter sign' (a sound resembling a distant helicopter) is present during stethoscope auscultation or electromyography of the trembling limb (*Video 1*). The weight-bearing lifting test shows decrease (78%) or ceasing (23%) (Liatis et al, 2022a) of the tremors. This test is a clinical test where orthostatic tremor decreases or discontinues after lifting and keeping the affected limbs air-floating (weight-bearing withdrawal); this occurs because orthostatic tremor is a postural tremor. Conscious electromyography while standing provides a final diagnosis of orthostatic tremor with pathognomonic muscle discharges of high frequency (>12 Hz). Treatment with antitremulous drugs (phenobarbital, gabapentin, clonazepam) has shown improvement of the tremors in 83% of dogs but this is usually partial improvement, as the tremor continues. It is important to note that Retrievers manifest a special form of primary orthostatic tremor which manifests later (older than 3.5 years old), and they are usually less pharmacoresponsive (Liatis et al, 2022a).

Orthostatic tremor-plus has been reported in a small group of dogs; two of them with cerebrocortical cerebrovascular accidents were suspected to manifest symptomatic orthostatic tremor (Liatis et al, 2022a). In comparison with dogs with primary orthostatic tremor, dogs with orthostatic tremor-plus were older at the onset of signs, included small breeds, had accompanying neurological signs and were more likely to have a negative weight-bearing lifting test. Treatment of the underlying disease is needed in dogs with orthostatic tremor-plus (Liatis et al, 2022a). Orthostatic tremor has not yet been reported in cats, although interestingly, a postural high-frequency tremor called 'campus syndrome' has been identified in Pietrain pigs (Richter et al, 1995; Wissel et al, 1997).

Benign idiopathic rapid postural tremor

In dogs, a form of progressive limb tremor called benign idiopathic rapid postural tremor (senile tremor) has been reported in older dogs, particularly in terrier breeds (*Video 1*), and has been speculated to represent essential tremor (Podell, 2004; Lowrie and Garosi, 2016a; De Lahunta et al, 2021). Although there are no studies in dogs, the authors have consistently observed it in terriers; in one terrier, conscious electromyography revealed muscle discharges of 3 Hz while standing. Treatment is not required (De Lahunta et al, 2021), and this tremor has not been reported in cats.

In humans, the most common tremor syndrome is essential tremor, which is a suspected genetic and progressive disease with two modes of onset of signs: young or old (Pan and Kuo, 2022). Four main pathophysiologies have been proposed for essential tremor (Pan and Kuo, 2022):

- Environmental exposures to β-carboline alkaloids and the consequent olivocerebellar hyperexcitation
- Cerebellar γ-aminobutiric acid deficiency
- Climbing fibre synaptic pathology with related cerebellar oscillatory activity
- Extra-cerebellar oscillatory activity.

A more recent study showed that locus coeruleus degeneration in the pons and cerebellar grey matter changes might lead in essential tremor (Lv et al, 2023).

Episodic non-intentional head tremor

Episodic head tremor is an isolated, non-intentional, directional (horizontal, vertical, rotatory) and usually distractible tremor of the head (*Video 1*) (Shell et al, 2015). When manifesting in the absence of neurological disease, it is considered idiopathic episodic head tremor. This has been reported in a variety of dogs, with Dobermanns and English Bulldogs having a suspected hereditary aetiology (Wolf et al, 2011; Guevar et al, 2014). It does not require treatment as it does not affect the quality of life of affected dogs (Shell et al, 2015). Although episodic head tremor has been usually considered a benign disease, there have been two case reports which described structural episodic head tremor secondary to pituitary mass (Fiorentino and Falzone, 2019; DuPont and Petesch, 2021). The authors are currently investigating a population with episodic head tremor and preliminary results suggest one-third of them had a structural thalamic or mesencephalic aqueduct lesion simulating head-bobble doll syndrome in humans (Liatis et al, 2023). Suspected idiopathic episodic head tremor has been reported in cats (Lowrie, 2021) and also observed by the authors (*Video 1*).

Action-related kinetic tremors

Intention tremors (cerebellar tremors)

A fine head and neck tremor which is augmented by the initiation of voluntary movement (for example, reaching for food or a toy) is called intention tremor and is associated with cerebellar disease (*Video 1*) (De Lahunta et al, 2021). It usually occurs from diffuse cerebellar disease rather than a focal cerebellar lesion (such as ischaemic cerebrovascular accident) and is accompanied by other cerebellar signs (De Lahunta et al, 2021). Any disease that could diffusely affect the cerebellum could produce intention tremors. More specific diseases are:

- Inflammatory or infectious (such as feline panleukopenia virus-associated cerebellar hypoplasia) (Stuetzer and Hartmann, 2014), meningoencephalitis of unknown aetiology (Nessler et al, 2020)
- Anomalous (for example, cerebellar aplasia or hypoplasia (Kornegay, 1986), Dandi-Walker-like malformation (Bernardino et al, 2015)
- Metabolic or toxic (such as metronidazole intoxication Tauro et al, 2018)

- Diffuse neoplastic (for example gliomatosis cerebri (Martin-Vaquero et al, 2012; Liatis et al, 2022b)
- Degenerative (hereditary ataxias (Stee et al, 2023), lysosomal storage diseases (Skelly and Franklin, 2002), acidurias (Abramson et al, 2003), mitochondrial encephalopathies (Gomes et al, 2021).

Hereditary ataxias with tremors include cerebellar cortical degeneration (cerebellar abiotrophy), spinocerebellar degeneration, cerebellar ataxias without substantial neurodegeneration but suspected functional dysfunction, multifocal degenerations with predominant (spino)cerebellar component including neuroaxonal dystrophies (Stee et al, 2023).

Steroid-responsive tremor syndrome

A special type of generalised tremors, that are not considered intentional, are seen in a disease of dogs called steroid-responsive tremor syndrome (*Video 1*) (Phillipps et al, 2022). Its name varies from 'white shaker disease', 'idiopathic generalised tremor syndrome' or 'idiopathic cerebellitis' (Wagner et al, 1997; Hazell et al, 2011; Phillipps et al, 2022). Its aetiology remains unknown ,although an immune-mediated origin is suspected; cerebellar involvement is considered possible but not exclusive (De Lahunta et al, 2021). Crossbreeds are overrepresented, and it is not a disease of white-coated dogs (Wagner et al, 1997; Phillipps et al, 2022). It usually affects young and small-sized dogs (Wagner et al, 1997; Hazell et al, 2011; Phillipps et al, 2022). These tremors have usually an acute onset and are usually accompanied (93.3%) by other cerebellovestibular neurological signs such as head tilt and hypermetria, and hyperthermia (22.7%) and gastrointestinal signs (41.3%) can be common (Phillipps et al, 2022). These tremors deteriorate with excitement, stress or exercise and improve during sleep. Magnetic resonance imaging of the brain is normal, and cerebrospinal fluid analysis usually reveals lymphocytic pleocytosis but can also be normal (Wagner et al, 1997; Hazell et al, 2011; Phillipps et al, 2022). Treatment includes immunosuppressive doses of steroids, along with muscle relaxants, and usually does not require chemotherapeutic drugs (Phillipps et al, 2022). The outcome is good following treatment; however, relapse can occur in 21.3% of patients and 13.2% of them can have residual neurological deficits (Phillipps et al, 2022).

Suspected steroid-responsive tremor syndrome has also been reported in two cats, one of which had a normal brain magnetic resonance imaging and both of which had normal cerebrospinal fluid analyses (Mauler et al, 2014).

Tremor due to myelin disorders

The myelin sheath in the central nervous system is formed by oligodendrocytes, whereas in the peripheral nervous sytem it is formed by Schwann cells (Van der Knaap and Bugiani, 2017). Myelin disorders include hypomyelination, dysmyelination, demyelination and myelinolytic diseases (Van der Knaap and Bugiani, 2017). Hypomyelinating (lack of myelin deposition which is biochemically normal) and dysmyelinating (deposition of structurally or biochemically abnormal myelin) diseases can cause tremors (Van der Knaap and Bugiani, 2017), whilst demyelinating diseases (loss of previously deposited myelin) rarely cause tremors – this mainly occurs when the demyelination is severe and diffuse (De Lahunta et al, 2021). In veterinary literature, hypo- or dysmyelination are causes of a tremor known as congenital tremor or shaker puppy syndrome (*Video 1*) (De Lahunta et al, 2021). In dogs, a genetic basis is suspected – although in some breeds, a genetic mutation has been found (De Lahunta et al, 2021). Although hypo- and dysmyelination have been reported in specific breeds (such as Springer Spaniel, Chow Chow, Weimaraner, Bernese Mountain

Table 1. The most common intoxicant agents that can cause twitches and tremors in dogs and cats.

Dogs	Cats
Medications Ivermectin 5-HTP (5-hydroxytryptophan) Moxidectin Amphetamines Zolpidem Pseudoephedrine Vilazodone Albuterol Risperidone Diphenhydramine Lamotrigine 5-fluorouracil (5-FU) Pramipexole Sertraline Baclofen Ibuprofen	**Medications** Mirtazapine Pregabalin Diphenhydramine Carbamazepine Enrofloxacin
Food Food with mycotoxins Chocolate Caffeine Xylitol Macadamia nuts	**Food** Food with mycotoxins
Rodenticides/insecticides Methomyl Metaldehyde Permethrin Disulfoton Bifenthrin DEET Strychnine	**Rodenticides/insecticides** Permethrins Avermectins (ivermectin, selamectin, moxidectin etc) Emodepside Piperazine DEET Methomyl Strychnine
Illicit drugs Methamphetamine Cannabis	**Illicit drugs** Amphetamines (illicit and ADHD medications) Ziprasidone
Miscellaneous agents Paintballs Salt dough Tobacco Activated charcoal	**Miscellaneous agents** Essential oils

Dog, Samoyed, Dalmatian, Lurcher and Terriers), any breed can be affected (Vandevelde et al, 1978; Griffiths et al,1981; Mayhew et al, 1984; Cummings et al, 1986; Kornegay et al, 1987; Pettigrew et al, 2007; Millan et al, 2010; De Lahunta et al, 2021).

The hallmark of semiology is generalised tremors, and these usually manifest from birth or as soon as the puppies can walk, but usually between 2–4 weeks old depending on the breed (De Lahunta et al, 2021; Lowrie, 2021). Possible accompanying neurological signs include bunny hopping, inability to stand and ambulate, cerebellar signs (hypermetria, intention tremors, wide based stance), epileptic seizures, menace response deficits and blindness, nystagmus or saccadic intrusions (De Lahunta et al, 2021; Lowrie, 2021). Due to remyelination, most of the breeds do improve between 2 weeks to 2 years of age, apart from the male Springer Spaniels (Griffiths et al, 1981). A genetic mutation has been found in Springer Spaniels (PLP1 gene) (Nadon et al,1990), Weimaraners (FNIP2 gene) (Pemberton et al, 2014) and Rat terriers (thyroid peroxidase gene) (Pettigrew et al, 2007) that has been associated with hypomyelination in these dogs. Hypomyelination also has been reported in Cretan hounds in association with intrauterine canine parvovirus-2 infection (Schaudien et al, 2010).

Hypomyelination has been reported in Siamese cats alongside behavioural changes and paraesthesia (De Lahunta et al, 2021).

Miscellaneous tremors

Other tremors have been reported or observed anecdotally that are not investigated yet. An episodic mandibular tremor manifested as teeth chattering has been described in older dogs and speculated to reflect a trigemino-trigeminal reflex (*Video 1*) (De Lahunta et al, 2021). The authors are investigating this type of tremor in Cavalier King Charles Spaniels and other breeds. The authors have also observed a dog with an episodic lingual tremor (*Video 1*) without concurrent neurological findings. Eye tremor, called opsoclonus, has been reported in dogs with steroid responsive tremor syndrome (Phillipps et al, 2022). Head with and without limb tremors have been reported briefly in paroxysmal non-kinesigenic dyskinesia in dogs (Lowrie and Garosi, 2016b).

Tremor has also been reported in dogs (Mehl et al, 2005) and cats (Blaxter et al, 1988) with hepatic encephalopathy due to portosystemic shunts, as well as in post-attenuation neurologic syndrome (Tisdall et al, 2000; Mullins and Creheut, 2023). It is currently unclear whether this tremor is an actual tremor due to manganese accumulation in the motor pathways or a twitch due to peripheral nerve hyperexcitability secondary to persistent hyperammonaemia.

Tremor-like syndromes in dogs and cats

Peripheral nerve hyperexcitability leads to twitches that vary in manifestation: fasciculations, cramps, myokymia, neuromyotonia, tetany and tetanus depending on the severity (Lowrie, 2021). Of them, the generalised fasciculations can mimic generalised tremors or even seizures. Generalised fasciculations do have variable amplitude and frequency which distinguish them from tremors (Lowrie et al, 2016a) and they tend to be present during sleep (Bashford et al, 2021).

KEY POINTS

- Tremors are involuntary, rhythmic, sinusoidal, oscillatory movements of a body part.
- Twitches are caused by peripheral nerve hyperexcitability and can be a result of toxicity and metabolic diseases among others.
- Steroid-responsive tremor syndrome and intoxications are the most common causes of generalised tremors and twitches in dogs.
- Tremors and twitches should be assessed thoroughly and systematically in order to be characterised and potentially reach a more specific diagnosis.

Dorsal horn neurons in the spinal cord under tight regulatory control by the central nervous system ensure muscular strength is coordinated, gradated and adaptable. Spontaneous activation of these cells and their axons can result in abnormal muscular twitching (Bashford et al, 2021). A common pathogenesis of peripheral nerve hyperexcitability in humans is pathology affecting the voltage-gated potassium channel (complex, such as leucine-rich glioma-inactivated 1, contactin-associated protein 2 and contactin 2 (Bashford et al, 2021)). The voltage-gated potassium channels regulate the movement of potassium ions across cell membranes. Activation leads to an increase in conductance and termination of action potentials, hyperpolarisation and hypoexcitability, whilst a block of these channels leads to depolarisation, prolongation of action potentials, repetitive firing and increases in transmitter release and endocrine activity (hyperexcitability) (Harris, 2009). Aetiologies for peripheral nerve hyperexcitability in humans include hereditary or immune-mediated channelopathies, motor neuron disease, polyneuropathies, metabolic, toxic, paraneoplastic or benign causes (such as anxiety) (Vanhaesebrouck et al, 2013; Bashford et al, 2021). In pets, aetiologies such as intoxications, metabolic disease, hereditary channelopathies and motor neuron disease have been described (Vanhaesebrouck et al, 2013; Lowrie and Garosi, 2016a), whilst neuropathies, immune-mediated channelopathies and benign causes have been speculated (Vanhaesebrouck et al, 2013).

Particularly in the toxic causes, these tremor-like phenomena are broadly described as 'tremors' in veterinary literature and the associated toxins as 'tremorgenic'; however, they were recently reclassified as twitches (Lowrie and Garosi, 2016a). 'Tremorgenic' intoxications usually include mycotoxins, pyrethrins, metaldehyde, avermectins and strychnine (Lowrie, 2021), while the American Society for the Prevention of Cruelty to Animals have published the most common 'tremorgenic' toxins for both dogs and cats (*Table 1*) (American Society for the Prevention of Cruelty to Animals, 2023a; 2023b). Metabolic diseases can also cause twitches in dogs and cats including hypoglycemia, hyperammonemia, hyperlactemia (*Video 1*), and electrolytic disturbances such as hypercalcaemia, hypocalcaemia, hyperphosphatemia, hyperchloremia and hypokalemia, while hypomagnesemia is most manifested as tetany (Di Bartola, 2012; Silverstein and Hopper, 2015).

Hereditary channelopathies have been reported in dogs with hereditary ataxias. This inherited form of peripheral nerve hyper-

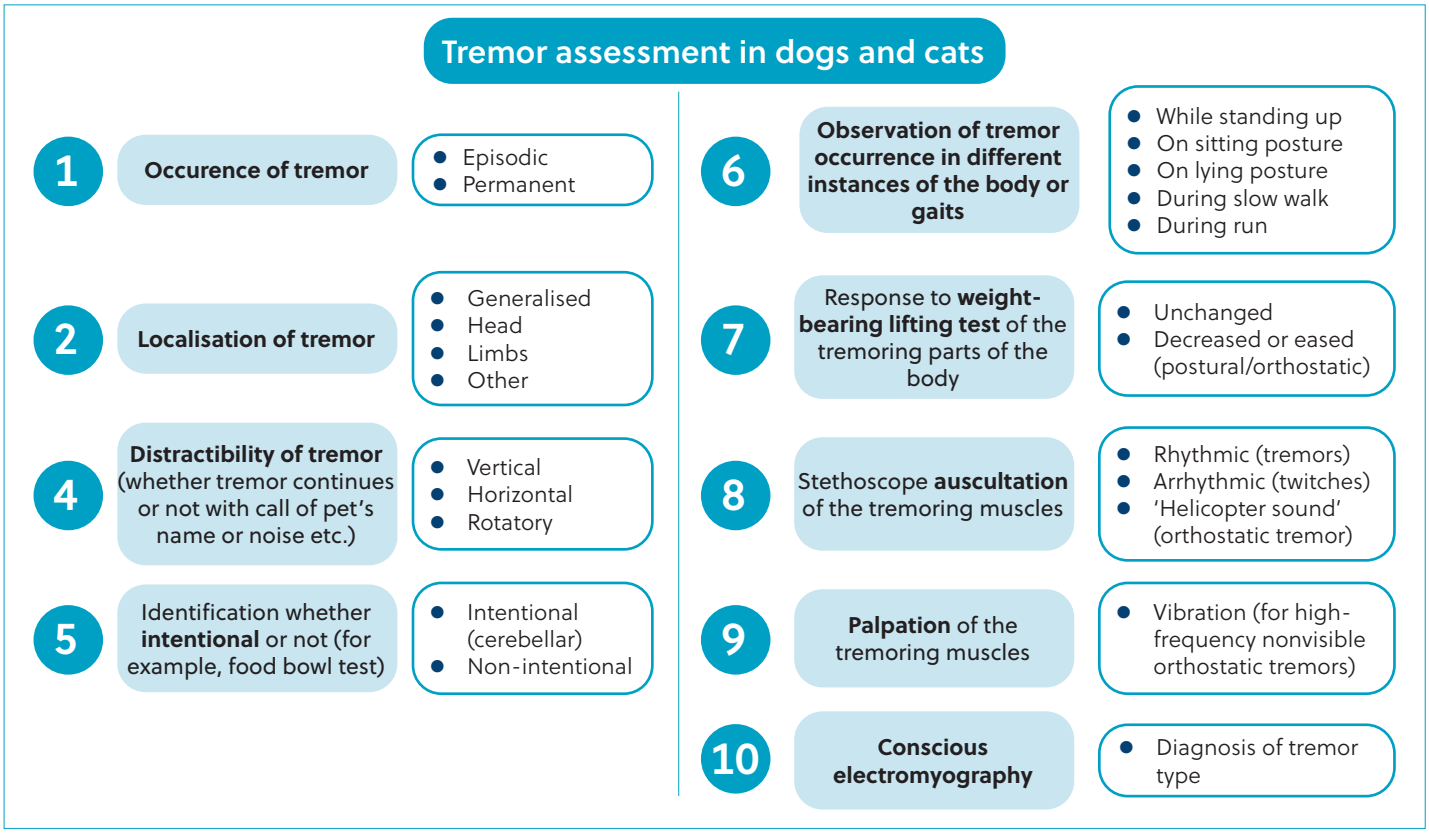

Figure 1. Suggested clinical assessment of tremor in dogs and cats.

excitability usually manifests as myokymia and neuromyotonia and not as generalised fasciculations in specific breeds (for example, Jack Russell Terriers) (Stee et al, 2023).

Although no specific studies have been published, it is highly speculated that cats in particular (but also dogs with polyneuropathies) do manifest twitches that interchangeably are reported as tremors (Bagley, 1992; Vanhaesebrouck et al, 2013; Lowrie and Garosi, 2016a). Although voltage-gated potassium channel antibodies have been found in some humans with polyneuropathies, and therefore peripheral nerve hyperexcitability might occur (Hart et al, 2002), the term 'neuropathic tremor' is now broadly used in literature to describe the semiology observed in polyneuropathies and a central origin has been speculated (Silsby et al, 2023). Neuropathic tremor is defined as tremor in the context of neuropathy in the absence of other causes and appears to be more common in demyelinating (most commonly chronic inflammatory demyelinating neuropathies) rather than axonopathies (Silsby et al, 2023). It has been speculated that cerebellar dysfunction secondary to distorted and delayed peripheral afferent inputs because of the demyelination leads to mistimed second agonist bursts enabling the antagonist muscle to act unopposed resulting in abnormal movement. As a consequence, the error in the limb position and velocity, when sent back to the cerebellum via demyelinated nerves, results in errors being perpetuated and therefore resulting in neuropathic tremor development (Silsby et al, 2023). It is obvious that there is a wide and interchangeable usage of terminology and debate in the pathophysiology of the twitches and tremors in polyneuropathies. The authors have observed twitches in cats with chronic polyneuropathies, however further studies are needed to investigate the nature of these tremors and twitches.

Clinical approach to a patient with tremor or tremor-like syndromes

The approach of an animal with a tremor or twitch should be performed in a thorough way to analyse clinical semiology, reach a more accurate diagnosis and form a plan.

Important information could be drawn from history (for example the ingestion of slug baits, moulded bread and the like), onset of clinical signs and accompanying presenting complaints. General physical and neurological examination findings should be recorded thoroughly, and it is crucial to perform a more specific tremor assessment derived from the neurological examination with or without additional video footage evaluation. Specifically, suggested steps for tremor assessment can be seen in *Figure 1*. Finally, progression over time is important clinical information to assist the clinician in orienting the differential diagnoses list.

Conclusions

Tremor and tremor-like syndromes in dogs and cats can have multiple aetiologies. There are historical, clinical and electrophysiological features that could assist the clinician in reaching a final diagnosis with an aim to organise the appropriate treatment plan and establish prognosis. Further studies need to be pursued as the tremors in dogs and cats are still under investigated. CA

Videos

Video 1 is available online at xxxxxxxx

Conflicts of interest

The authors declare that there are no conflicts of interest.

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