Clinical approach of tremors in dogs and cats

De klinische benadering van tremoren bij honden en katten

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ABSTRACT

Tremors are movement disorders that resemble involuntary rhythmic oscillatory sinusoidal movements of a body part. Twitches are the manifestation of peripheral nerve hyperexcitability and have variable frequencies and amplitudes. Tremor syndromes are a relatively common presentation in dogs and cats in clinical practice. It is important for the practitioner to be aware of the most common tremor syndromes, and how to recognize, diagnose and treat them. Taking a thorough clinical history and performing a detailed clinical and neurological examination, including tremor assessment are cornerstone processes for reaching a diagnosis. Tremors can be generalized, affecting the whole body and limbs, or focal, affecting specific parts of the animal. The most common etiologies of generalized tremors in dogs are corticosteroid-responsive tremor syndrome and intoxication, e.g. metaldehyde, mycotoxin. Common focal canine tremors include idiopathic episodic head tremor and orthostatic tremor. The most common cause of generalized tremors in cats is permethrin intoxication.

SAMENVATTING

Tremoren zijn bewegingsstoonissen die lijken op onwillekeurige ritmische oscillerende en sinusiadale bewegingen van een lichaamsdeel. “Twitches” of ‘spiertrekkingen’ zijn de uitdrukking van perifere zenuwovergevoeligheid en hebben variabele frequenties en amplitudes. Tremorsyndromen zijn een relatief vaak voorkomende klinische presentatie bij honden en katten in de praktijk. Het is belangrijk voor de practicus om op de hoogte te zijn van de meest voorkomende tremorsyndromen, hoe deze worden herkend, gediagnosticeerd en behandeld. Een volledige anamnese en een gedetailleerd klinisch en neurologisch onderzoek, inclusief beschrijving van de tremor, zijn essentieel voor het stellen van een diagnose. Tremoren kunnen gegeneraliseerd zijn, wanneer ze over het hele lichaam en de ledematen aanwezig zijn, of focaal, wanneer ze een specifiek lichaamsdeel treffen. De meest voorkomende etiologie van generaliseerde tremoren bij de hond zijn het corticosteroïd-responsief tremorsyndroom en intoxicatie, zoals metaldehyde- en mycotoxine-intoxicatie. Vaak voorkomende focale tremoren bij honden zijn idiopathische hoofdtremor en orthostatische tremor. De meest voorkomende oorzaak van gegeneraliseerde tremoren bij katten is permethrine-intoxicatie.

INTRODUCTION

Tremor syndromes in dogs and cats are movement disorders that include tremors and twitches, which have been faintly investigated in veterinary neurology. 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 as resting or action-related. Resting tremors refer to tremors occurring when the tremoring body part is completely supported

against gravity without voluntary muscle contraction. They have not been reported in veterinary medicine yet (Lowrie and Garosi, 2016). Action-related tremors can be divided into postural, which occur while maintaining a posture against gravity (e.g. orthostatic tremor), and kinetic tremors occurring during active movements, such as goal-directed movements (e.g. intention tremor) (Lowrie and Garosi, 2016). Twitches, such as generalized fasciculations, can mimic tremors but they have a variable amplitude and frequency and are caused by peripheral nerve hyperexcitability (Cerda-Gonzalez et al., 2021; Lowrie and Garosi, 2016a). Although tremors have a uniform frequency in contrast to twitches, the distinction between tremors and twitches is clinically challenging. For this reason, in this clinical review the umbrella term tremors is used to refer to both actual tremors and twitches.

Although the clinical approach to tremors is discussed in this review, the first question that needs to be answered is if the tremors are generalized (i.e. affecting the whole body) or whether they are focal (i.e. affecting a specific part of the body). A basic understanding of the most common tremor syndromes can subsequently assist in identifying the most likely diagnosis in the patient.

GENERALIZED TREMORS

Despite their dramatic presentation, only a limited number of conditions result in generalized tremors. By far, the most common causes of generalized tremors in dogs are intoxications and corticosteroid-responsive tremor syndrome (CRTS) (Wagner et al., 1997). As CRTS is rare in cats, generalized tremor should alert the clinician for intoxication (e.g. permethrin) as a major differential diagnosis, and supportive treatment should be initiated without delay to decrease the risks of mortality.

Corticosteroid-responsive tremor syndrome

Generalized tremors are seen in CRTS (Phillipps et al., 2022). This disease has had alternative names in the past such as ‘little white shaker disease’, ‘idiopathic generalized tremor syndrome’ or ‘idiopathic cerebellitis’ (Wagner et al., 1997; Hazell et al., 2011; Phillipps et al., 2022). This disease was previously called ‘little white shaker disease’ as it was believed to affect small breeds with a white coat. It has however become apparent that dogs of any coat color and size can be affected (Phillipps et al., 2022). Its etiology remains unknown although an immune-mediated origin is suspected (De Lahunta et al., 2021). Pathological studies can reveal a mild lymphocytic inflammation, most predominantly affecting the cerebellum (De Lahunta et al., 2021). Crossbreeds are over-represented (Wagner et al., 1997; Phillipps et al., 2022) and most affected dogs are young with a median age of 1.4-year-old (Phillipps et al., 2022), which agrees with previous studies (Wagner et al., 1997; Hazell et al., 2011). These tremors usually have an acute onset and can be accompanied (93.3%) by other cerebellovestibular signs such as head tilt, ataxia, nystagmus, opsoclonus and hypermetria (Phillipps et al., 2022). Increased muscle activity can occasionally result in hypermetria. Titubation can also be seen in dogs with CRTS as in other cerebellar diseases; titubation describes a truncal sway or ‘truncal ataxia’ and some authors consider it as a ‘slow’ tremor (De Lahunta et al. 2021; Phillipps et al., 2022). In the study by Phillipps et al. (2022), gastrointestinal signs, such as vomiting, retching, regurgitation, hyporexia/anorexia, diarrhea, or abdominal pain, preceding the occurrence of tremors, were reported in 41.3% of affected dogs. The relationship between gastrointestinal and neurological signs remains currently unclear. These tremors worsen with excitement, stress or exercise and improve when the animal is completely relaxed, when sleeping for instance, or under sedation or general anesthesia. Magnetic resonance imaging of the brain is normal, and cerebrospinal fluid analysis can be normal or reveal a mild lymphocytic pleocytosis, or mildly increased proteins (Wagner et al., 1997; Hazell et al., 2011; Phillipps et al., 2022). Treatment includes immunosuppressive doses of corticosteroids (with a starting dose of prednisolone at 2 mg/kg q24h with a median treatment time of six months), possibly combined with muscle relaxants (such as diazepam 0.5 mg/kg IV/PO q8h), and usually does not require additional immunomodulating or chemotherapeutic drugs (Phillipps et al., 2022). The outcome is good following treatment; however, in the study by Phillipps et al. (2022), relapse occurred in 21.3% of patients and 13.2% of them had residual neurological deficits, such as tremors when excited or jaw chattering .

Corticosteroid-responsive tremor syndrome causing generalized tremors 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. These cats were treated with prednisolone, and both improved, although one of them had a relapse (Mauler et al., 2014).

Acute intoxication

Acute intoxication can lead to generalized tremors (twitches - fasciculations) of variable amplitude and frequency (Lowrie and Garosi, 2016), which tend to persist during sleep (Bashford et al., 2021).

Tremorgenic intoxicant agents in dogs and cats include mycotoxins usually originating from moldy food, permethrines, metaldehyde, avermectins and strychnine (Yas-Natan et al., 2007; Merola et al., 2009; Kormpou et al. 2018; Lowrie, 2021; American Society for the Prevention of Cruelty to Animals, 2023).

The diagnosis of acute neuro-intoxications is largely

based on the clinical history (witnessed or suspected exposure to intoxicant agents), in combination with compatible clinical signs (tremors, epileptic seizures, cerebellovestibular, gastrointestinal or renal signs, clinicopathological findings) and the improvement after supportive treatment within 24-48 hours. Treatment includes systemic stabilization and maintenance of hydration and normovolemia with intravenous fluid treatment. Depending on the clinical presentation, symptomatic treatment include antiseizure drugs in case of epileptic seizures, muscle relaxants in case of tremors (e.g. diazepam, methocarbamol), control of body temperature, decontamination (e.g. activated charcoal within 24 hours from exposure), and emesis induction within the first two hours of toxin ingestion if indicated (Pittman et al., 2012). Intravenous lipid emulsion has been broadly used as an antidote in lipophilic drug intoxication in dogs. In a study in 53 dogs with suspected tremorgenic mycotoxicosis, 96% of cases improved clinically within a median time of four hours after the administration of intravenous lipid emulsion (Kormpou et al., 2018). Presumptive mechanisms of action of intravenous lipid emulsion includes (a) sequestering the toxic substance in a new lipid compartment within the intravascular space (known as a 'lipid sink'), (b) improving mitochondrial function by providing a source of fatty acids for metabolism, (c) providing cardiomyocytes with energy substrate, and (d) improving cardiomyocyte function by increasing intracellular calcium (Becker and Young, 2017). Intravenous lipid emulsion appears to be overall a safe and useful antidote for known intoxications with no side effects other than lipemia (Becker and Young, 2017; Kormpou et al., 2018). Some of the most common intoxications are described below.

Permethrin intoxication in cats

Although permethrin is considered safe for most mammals, cats may be susceptible to intoxication. It has been hypothesized that cats may develop intoxication due to a deficiency in glucuronidyltransferase, which may delay metabolism of the agent (Malik et al., 2017). Permethrin is a neurotoxicant, acting on voltage-dependent sodium channels (Sutton et al., 2007).

The main source of intoxication in cats is the transdermal application of anti-ectoparasitic products ('spot-on') labelled for use in dogs (Malik et al., 2017). Occasionally, exposure can be through secondary direct or indirect contact of the cat with a dog that recently had application of the anti-ectoparasitic on its skin (Malik et al., 2017). The majority of cats (86-87.8%) manifests with generalized tremors/twitches; however epileptic seizures, hyperthermia, hypersalivation, ataxia, mydriasis and temporary cortical blindness have also been reported (Sutton et al., 2007; Boland et al., 2010). The duration of increased muscle activity can be long, with convulsions lasting on average 38.9 hours and tremors 32 hours (Sutton et al., 2007). Recovery from the tremors in cats occurs within two to three days but in some cases, it takes five to seven days (Boland and Angles, 2010). Complications can occur in around 33% of cats and may include hypothermia, electrolyte abnormalities, aspiration pneumonia, hypoproteinemia and other signs (Boland and Angles, 2010). The mortality rate has been reported around 10.5% (Sutton et al., 2007).

Treatment includes decontamination (e.g. bathing, intravenous fluid treatment, activated charcoal, intravenous lipid emulsion), antiseizure drugs (e.g. intravenous phenobarbital, intravenous midazolam constant rate infusion, intravenous propofol constant rate infusion), muscle relaxants (e.g. diazepam, methocarbamol) and supportive care (e.g. sedation, maintain temperature) (Boland et al., 2010; Muentener et al., 2013; Ceccherini et al., 2015).

Mycotoxin intoxication

Mycotoxin intoxication, traditionally called 'tremorgenic' intoxication, is caused by ingestion of moldy foods, including grains, walnuts, almonds and peanuts, as well as nonspecific garbage (Barker et al., 2013). The most common tremorgens in dogs are penitrem A and roquefortine C, with *Penicillium crustosum* contamination the most commonly identified source (Barker et al., 2013). The mechanism of action is not widely known; this can vary depending on the type of mycotoxin, which can also act synergistically. It is hypothesized that tremorgenic mycotoxins interfere with inhibitory neuroreceptors and enhance excitatory amino acid neurotransmitter release mechanisms leading to neurological signs (Bates, 2022). The hallmark of clinical manifestation is generalized tremors, that can be so severe that they can mimic status epilepticus. Additional clinical and neurological signs may be hyperthermia, tachypnea and hypersalivation, mydriasis, nystagmus, generalized hyperesthesia, (Barker et al., 2013). Treatment is similar to permethrin intoxication. In the study by Kormpou et al. (2018), an improvement in 96% of dogs with mycotoxicosis after intravenous lipid emulsion was demonstrated. The prognosis is good if no severe systemic complications occur (Barker et al., 2013).

Metaldehyde intoxication

Metaldehyde is a molluscicide that is used commercially in snail and slug baits most commonly in the form of granules but also as liquid, powder or pellets (Yas-Natan et al., 2007). The mechanism of action of metaldehyde is not completely known; however, in experimental studies, metaldehyde has led to an increase in monoamine oxidase activity and to a decrease in gamma-aminobutyric acid, norepinephrine and 5-hydroxytryptamine concentrations, which has led to neuronal excitation and a decreased seizure threshold (Yas-Natan et al., 2007). Although epileptic seizures are the most common clinical sign, genera-

lized tremors occur in 55% of dogs with metaldehyde intoxication (Yas-Natan et al., 2007). Other clinical signs can include hyperthermia, tachycardia, hypersalivation and diarrhea. As the granules are green or blue, green or blue color might be observed in the gastrointestinal content (Yas-Natan et al., 2007; De Roma et al., 2017). The treatment is similar to the treatment of permethrin intoxication (Yas-Natan et al., 2007). Dogs with metaldehyde intoxication have an increased risk of aspiration pneumonia due to decreased consciousness among other neurological deficits and the combination of vomiting and prolonged general anesthesia performed for the gastric lavage (Teichmann-Knorrn et al., 2020). Hemodialysis -although limited in availability to most of the vet practices- has been reported to significantly decrease the requirement for anesthesia and length of hospitalization in dogs with metaldehyde intoxication; additionally, aspiration pneumonia occurs less often in hemodialyzed patients likely due to the short duration of anesthesia (Teichmann-Knorrn et al., 2020). The survival rate of dogs with metaldehyde intoxication treated with supportive treatment has been reported to be 83% (Yas-Natan et al., 2007).

Shaking puppy syndrome (hypomyelination/dysmyelination)

Although rare, disorders of myelin such as hypomyelination or dysmyelination can cause tremors (Van der Knaap and Bugiani, 2017). In the veterinary literature, these diseases are known as congenital tremor, shaking puppy syndrome or shaker syndrome (De Lahunta et al., 2021). A genetic basis is suspected as a genetic mutation has been found in specific canine breeds (De Lahunta et al., 2021). Specific breeds such as the springer spaniel, chow chow, Weimaraner, Bernese mountain dog, Samoyed, Dalmatian, lurcher and terriers have been reported with the disease; however, 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; Millán et al., 2010; De Lahunta et al., 2021).

Generalized tremor is the most prominent clinical sign, and it usually manifests from birth or as soon as the puppies can walk, usually between two to four weeks old (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 cortical blindness, nystagmus or other abnormal eye movements (De Lahunta et al., 2021; Lowrie, 2021). Due to remyelination, most of the breeds improve spontaneously between two weeks to two 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 (TPO gene) (Pettigrew et al., 2007). Hypomyelination has also been reported in Cretan hounds in association with intrauterine canine parvovirus-2 infection (Schaudien et al., 2010) and in Siamese cats alongside behavioral changes and paraesthesia (De Lahunta et al., 2021).

The diagnosis is based on history, compatible clinical signs in susceptible breeds, and clinical progression. A specific treatment is currently not available and affected animals usually improve spontaneously with age.

Metabolic diseases

Metabolic diseases can cause tremors (peripheral nerve hyperexcitability) in dogs and cats. Of them, hypoglycemia, hyperammonemia, hyperlactemia, and electrolytic disturbances, such as hypercalcemia, hypocalcemia, hyperphosphatemia, hyperchloremia, hypokalemia are common (Di Bartola, 2012; Silverstein and Hopper, 2015). Tremors have 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 with post-attenuation neurologic syndrome (Tisdall et al., 2000; Mullins and Serrano 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 hyperammonemia.

The diagnosis of metabolic-related tremors is based on the diagnosis of the underlying metabolic disease. Baseline clinicopathological tests include hematology, serum biochemistry including electrolytes, ammonia and bile acid stimulation test, and urinalysis. In some metabolic diseases such as thiamine deficiency, clinicopathological tests may be unremarkable, and therefore dietary history is of crucial importance. Treatment of the underlying condition is imperative to resolve the tremors and in some conditions, it might include supplementation of a substance (e.g. glucose, calcium) (Groman, 2012; Idowu and Heading, 2018). Supportive treatment is also needed and includes control of body temperature, administration of muscle relaxants, active cooling, maintenance of hydration and normovolemia (e.g. intravenous fluid treatment), antiseizure drugs in case of epileptic seizures, hepatoprotectants in case of hepatopathy, or a hypoallergenic diet depending on the etiology (Tisdall et al., 2000; Mullins and Serrano Creheut, 2023).

Orthostatic tremors (generalized)

Orthostatic tremors are rare postural tremors, which occur in dogs exclusively while standing (Liatis et al., 2022). This type of tremor is associated with pathognomonic electrical discharges of the muscle of high frequency (>12 Hz) on conscious electromyography (Liatis et al., 2022). Although it predominantly affects the pelvic limbs, it can progress to the thoracic limbs and even involve the head and becomes

therefore generalized (Liatis et al., 2022). Orthostatic tremor will be further discussed below.

FOCAL TREMORS

Focal tremors affect specific parts of the body such as the head or pelvic limbs. These types of tremors are not well described in the veterinary literature. Tremors affecting other body parts, such as the mandible, have been anecdotally reported. Focal tremors can be classified as (a) focal tremors affecting the head and (b) focal tremors affecting the pelvic limbs. The most common causes of focal tremors in dogs are intention tremors and idiopathic episodic head tremor.

Focal tremors affecting the head

The most common tremor affecting the head in both dogs and cats is intention tremor. Idiopathic episodic head tremor can be seen occasionally in dogs and rarely in cats (Shell et al. 2015; Lowrie, 2021), whilst structural episodic head tremor is rare and is usually accompanied by other neurological signs (Liatis et al., 2023a). Dystonic head tremor is seen in dogs with cervical dystonia as part of the semiology of paroxysmal dyskinesia in dogs (Liatis et al., 2023b). Rarely, in severe canine cases, orthostatic tremor can affect the head as a part of a generalized tremor presentation (Liatis et al., 2022).

Intention tremors (cerebellar tremors)

A subtle fine tremor affecting the head and neck when a voluntary movement is initiated is called intention tremor. Reaching a goal, such as a toy or food, can elicit this tremor, hence the characterization of 'intention'. The tremor disappears when the movement is continued and therefore typically lasts only a few seconds. Intention tremor has been associated with cerebellar disease (De Lahunta et al., 2021). It usually occurs as a result of diffuse cerebellar disease rather than a focal cerebellar lesion (such as ischemic cerebrovascular accident) and is most typically accompanied by other cerebellar signs (De Lahunta et al., 2021). Any disease that could diffusely affect the cerebellum, could produce intention tremors. Conditions that preferentially affect the cerebellum include feline panleukopenia virus associated cerebellar hypoplasia (Stuetzer and Hartmann, 2014), cerebellar aplasia or hypoplasia (Kornegay, 1986), Dandy-Walker-like malformation (Bernardino et al., 2015), metronidazole intoxication (Tauro et al., 2018), cerebellar abiotrophy, termed now cerebellar cortical degeneration, and hereditary ataxias (Stee et al., 2023). The diagnosis of this type of tremor is based on its characteristic features and the presence of other cerebellar signs. It is important to highlight that this tremor is not present when the animal is at rest, and therefore it is necessary to elicit it with offering a toy, food or water to the patient. When approaching the dog with the object (e.g. toy or bowl), a short fine head tremor is elicited when the animal starts moving towards the object. The tremor disappears when the animal has reached the object. This tremor is usually subtle and short-lived, which might be helpful in distinguishing this type of tremor from other head tremors. Treatment is based on the nature of the underlying condition.

Episodic (non-intentional) head tremor

Episodic head tremor is a focal, non-intentional, directional (horizontal, vertical, rotatory) and usually distractible tremor of the head (Shell et al., 2015). When manifesting in the absence of neurological disease, it is considered an idiopathic episodic head tremor. Alternative names for this condition are idio-pathic head tremor syndrome, idiopathic episodic head tremor syndrome or head bobbing. This has been reported in a variety of dogs, with Dobermans and English bulldogs having a suspected hereditary etiology (Wolf et al., 2011; Guevar et al., 2014). This tremor typically affects young dogs (around two years old), is episodic, may usually be distracted by touching, calling their name or offering a toy, has a direction (vertical, horizontal or rotatory), and during its course, the dog is conscious. The tremor episode has a median duration of six minutes but could last from few seconds to six hours (Liatis et al., 2023a). Although some owners have reported potential triggers such as stress or exercise, no identifiable trigger has been found in the majority of dogs (Shea et al., 2012; Guevar et al., 2014; Liatis et al., 2023). Investigations including MRI of the head and cerebrospinal fluid analysis are expected to be normal (Liatis et al., 2023a). The diagnosis is based on signalment (over-represented breeds), clinical signs (characteristic head tremor in absence of other neurological signs) and lack of structural findings on MRI. Treatment is not typically recommended as these tremors do not seem to affect the quality of life of affected dogs (Shell et al., 2015). Episodic head tremor can decrease in frequency as the dog grows up (Shell et al., 2015; Liatis et al., 2023). Treatment trials have been performed with phenobarbital, imepitoin, potassium bromide, gabapentin or levetiracetam, but no consistent positive response has been reported for the majority of dogs (Shell et al., 2015; Schneider et al. 2020; Liatis et al., 2023a). The evaluation of treatment is further complicated by the fact that a substantial proportion experiences spontaneous improvement or resolution of clinical signs. It has been reported that 50% of affected English bulldogs demonstrated a spontaneous resolution of tremor episodes (Guevar et al., 2014). Suspected idiopathic episodic head tremor has also been reported in cats (Lowrie, 2021).

Although episodic head tremor has usually been considered a benign disease, in a recent study, some dogs with a recent onset of episodic head tremor and accompanying neurological signs were diagnosed with an underlying structural brain disease, which was hence

characterized as structural episodic head tremor (Liatis et al., 2023a). In those cases, episodic head tremor is associated with a structural thalamic or mesencephalic aqueduct lesion simulating head-bobble doll syndrome in humans (Reddy et al., 2014; Ure et al., 2016). Structural episodic head tremor tend to affect older dogs, belonging to atypical breeds and often display accompanying neurological signs. In those dogs diagnosed with meningoencephalitis, episodic head tremor is reversible as soon as immunosuppressive or antibiotic treatment is initiated (Liatis et al., 2023a).

Dystonic head tremor

Dystonia is a sustained, slow, involuntary contraction of agonist and antagonist muscles of a body region producing abnormal postures and/or involuntary movement of portions of the body along a longitudinal axis. Dystonia is the major neurological sign of the disease called paroxysmal dyskinesia (Cerda-Gonzalez et al., 2021). Dystonic head tremor is the tremor of the head in dogs that are concurrently affected by dystonia, and is predominantly a postural/kinetic focal tremor with irregular amplitudes and variable frequencies (mainly <7 Hz). The pathophysiology of dystonic tremor is unknown, but basal nuclei pathology has been postulated (Fasano et al., 2014). This tremor has been recently described in 43.6% of dogs diagnosed with paroxysmal non-kinesigenic dyskinesia along with cervical dystonia (Liatis et al., 2023b). This type of tremor does not occur as an isolated event, but as part of a more generalized movement disorder. Affected dogs therefore display other types of abnormal movements at the same time they demonstrate head tremors. Poodle or Poodle-cross is the most commonly affected breed. The diagnosis is based on clinical presentation (head tremor has been reported in conjunction with cervical dystonia and the diagnosis of paroxysmal dyskinesia) (Liatis et al., 2023b). Empiric treatments (e.g. levetiracetam, gabapentin, potassium bromide, imepitoin) have not resulted in consistent improvement (Schneider et al., 2020; Liatis et al., 2023b).

Focal tremors affecting the pelvic limbs

Focal tremors of the pelvic limbs consist of physiologic tremors, benign idiopathic rapid postural tremors (BIRPT), orthostatic tremors or neuropathic tremors. Physiologic tremor, BIRPT and orthostatic tremors are postural tremors. Postural tremors occur while maintaining a posture against gravity, in contrast to kinetic tremors (e.g. intention tremors) that occur during active movement (Lowrie and Garosi, 2016).

Physiologic tremors

In humans, physiologic tremor can be observed in normal individuals during enhanced muscle activity such as while exercising or immediately thereafter, fatigue, anxiety or conditions associated with a hypermetabolic state, probably related to increased sympathetic activity (Lenka and Jankovic, 2021). This tremor type has not been widely discussed in the veterinary literature; however, it has been previously associated with stress or pain in dogs (Platt and Olby, 2014).

Orthostatic tremors in dogs

Orthostatic tremors are rare postural tremors that predominantly affect the pelvic limbs, exclusively while standing with pathognomonic high frequency muscle discharges (>12 Hz) on conscious electromyography (Liatis et al., 2022). Their pathophysiology is unknown, but a central oscillator, located in the brainstem or cerebellum, has been hypothesized to generate orthostatic tremors and are considered to represent a neurodegenerative disease (Benito-Leon and Domingo-Santos, 2016; Schöberl et al., 2017).

Although orthostatic tremors were firstly reported in Great Danes (Garosi et al., 2005), they can occur in other breeds as well. They appear to predominantly affect purebred giant or large breed dogs. They usually occur in young dogs between nine months and two years old (Liatis et al., 2022). In 62% of dogs, the tremors progress in intensity or expand to the thoracic limbs, trunk and head, and a genetic predisposition has been suspected (Liatis et al., 2022). Orthostatic tremor is usually primary when it manifests as a sole sign with unremarkable diagnostic tests. When it is concomitant with other neurological, electrophysiological or imaging findings, it is classified as orthostatic tremor-plus (Liatis et al., 2022).

The semiology of primary orthostatic tremors includes tremors usually affecting the pelvic limbs; 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 characterized by alternating weight from one limb to another in an attempt to avoid the disturbing tremors. Additional signs include difficulty in sitting or rising, wide-based stance, wide-based gait on slow walk, difficulty in maintaining posture during specific activities (e.g. eating, drinking) and in severe cases, the tendency to fall (postural instability) (Liatis et al., 2022).

A final diagnosis of orthostatic tremor is confirmed on conscious electromyography while standing, where there are pathognomonic muscle discharges of high frequency (>12 Hz). However, there are also clinical findings that can help to highly suspect orthostatic tremor in clinical practice. A ‘helicopter sign’ (i.e. a sound resembling a distant helicopter) is present during stethoscope auscultation of the trembling limb. The weight-bearing lifting test is considered positive as it shows decrease (78%) or resolution (23%) of the tremors (Liatis et al., 2022). The weight-bearing lifting test is a clinical test which includes lifting of the trembling parts of the body (i.e. pelvic limbs) up in the

air and observation of gross changes in the frequency of the tremors. If the tremors are obviously decreased or discontinue, the test is considered positive. If the tremors are unchanged, the test is considered negative. In orthostatic tremor cases, the test is considered positive; this occurs because orthostatic tremor is a postural tremor. Treatment could include phenobarbital, gabapentin or clonazepam. In a recent study, 83% of dogs treated with one of these medications showed (usually partial) improvement. If not treated, orthostatic tremor may progress to the thoracic limbs, trunk and head (Liatis et al., 2022).

Retriever breeds may have a special form of primary orthostatic tremor which manifests later (older than 3.5 years old), and they are usually less pharmacoresponsive compared to other breeds (Liatis et al., 2022).

Orthostatic tremor-plus has been reported in a small group of dogs, two of which with cerebrocortical vascular accident as an underlying condition (Liatis et al., 2022). In comparison with dogs with primary orthostatic tremor, dogs with orthostatic tremor-plus are older at the onset of signs, they are of smaller breeds, have accompanying neurological signs and are more likely to have a negative weight-bearing lifting test. Treatment of the underlying disease is suggested for dogs with orthostatic tremor-plus. In the small number of reported cases, treatment of the underlying condition, resulted in an improvement, but not a resolution of the tremors (Liatis et al., 2022).

Benign idiopathic rapid postural tremor (senile tremors) in dogs

In dogs, BIRPT is a form of progressive, usually pelvic limb tremor. It has also been termed as senile tremor and it has usually been observed in older dogs, particularly in terrier breeds (Podell, 2004; Lowrie and Garosi, 2016; De Lahunta et al., 2021). It has been speculated to be similar to essential tremor in humans and is of lower frequency than orthostatic tremors (Lowrie and Garosi, 2016). Clinical differentiation of BIRPT from the orthostatic tremor requires conscious electromyography and is based on the lower frequency of it compared to the high one in orthostatic tremor (Liatis et al., 2022). Auscultating a 'helicopter sign' on the muscles would be expected in these cases as well, as these tremors are postural similar to orthostatic. Additionally, there is a difference in age at the onset of the tremors (older for BIRPT, younger for orthostatic tremor) and in breeds (terriers for BIRPT). This tremor is benign, it does not usually affect the quality of life, and no further treatment is usually required.

Neuropathic tremor

Neuromuscular disease, and specifically neuropathies, has been associated with tremor, usually referred to as 'neuropathic tremor' in humans. 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). Voltage-gated potassium channel antibodies have been identified in human polyneuropathies and thus the 'tremor' might reflect peripheral nerve hyperexcitability rather than an actual tremor (Hart et al., 2002). Tremors have also been reported in dogs and cats with neuromuscular disease (Platt and Olby, 2014). They have also been reported in ischemic neuromyopathy secondary to aortic thormboembolism as a result of poor perfusion (Platt and Olby, 2014). Particularly in cats diagnosed with polyneuropathies twitches, usually described as tremors, are traditionally reported in the literature (Bagley, 1992; Vanhaesebrouck et al., 2013; Lowrie and Garosi, 2016). These tremors have not been extensively studied in the veterinary literature; however, neuromuscular disease should be considered in the differential diagnoses list of tremors of the pelvic limbs.

Miscellaneous tremors

An episodic mandibular tremor manifested as teeth chattering has been described in older dogs and is speculated to reflect a trigemino-trigeminal reflex (De Lahunta et al., 2021). More recently, a retrospective study described in depth an episodic mandibular tremor in dogs, mostly seen in young adult Cavalier King Charles spaniels, that could be associated with a benign focal movement disorder or a manifestation of pain (Liatis et al., 2024). Eye tremor, called opsoclonus, has been reported in dogs with CRTS (Phillipps et al., 2022). Not only dysignic head tremor, but also limb tremors have been reported briefly in paroxysmal nonkinesigenic dyskinesia in dogs (Lowrie and Garosi, 2016). Although other movement disorders such as myokymia (i.e. contraction of facial or limb myofibers, often exhibiting an undulation/vermicular movement of the skin overlying the affected muscle) or myoclonus (i.e. brief shock-like jerks resulting from the sudden involuntary contraction or relaxation of muscles) generally do not look like tremors (Cerda-Gonzalez et al. 2021), they should be occasionally considered when assessing a patient.

CLINICAL APPROACH TO TREMORS

History

Obtaining a thorough clinical history is a cornerstone for the investigation of tremors. Possession or access to drugs or intoxicant agents might indicate intoxication (e.g. human drugs, access to moldy food). Outdoor access might indicate access to intoxicant agents (e.g. lawn treatment (organophosphates, slug baits–metaldehyde), lead weights, toxic plants, mush-

rooms). The time of onset of the tremors is of great importance: since birth (e.g. cerebellar hypoplasia), two to six weeks of age (e.g. hypomyelination), adult-onset, elderly-onset; as well as whether the manifestation was acute (e.g. inflammatory/toxic disease) or chronic (e.g. degenerative). Breed information is also important, as there are certain breeds over-represented in specific tremor syndromes: Bulldogs and Dobermans in idiopathic episodic head tremor (Wolf et al., 2011; Guevar et al., 2014), Great Danes and retrievers in orthostatic tremors (Liatis et al., 2021), or terrier breeds in BIRPT (Podell et al., 2004).

Tremor analysis

The results of thorough general physical and neurological examinations can reveal crucial information about the tremoring patient (https://youtu.be/GHSsOIbhPI - video compilation of tremor syndromes in dogs and cats). Tremor analysis should be based on observation (eventually video footage of the event in case of episodic tremors) and hands-on examination. Suggested tremor assessment should include: (a) occurrence of tremor (e.g. episodic or continuous), (b) localization of the tremor (e.g. generalized, head, pelvic limbs), (c) intentionality (e.g. intentional tremor or non-intentional), (d) instances during which the tremor is manifested (i. e. while standing up), (e) response to weight-bearing lifting test, (f) auscultation of the trembling body part for a 'helicopter sign' and (g) palpation of the trembling limbs (i. e. to check for high frequency palpable tremors that are not visible by the naked eye) (Figure 1).

When creating a list of differential diagnoses, a clinician should follow a question-based approach as per below:

1. Is the tremor (1) generalized affecting the whole body, (2) focal predominantly affecting the head or (3) focal predominantly affecting the pelvic limbs?

By identifying the localization of the tremor on the body, the differential diagnoses list is immediately narrowed down. Now, the clinician can focus on specific aspects of the clinical presentation to recognize the most likely diagnosis.

2. Are the tremors the only neurological sign or are there other accompanying neurological findings?

If the tremors are the only neurological sign in the patient, then it is more likely that the dog has an idiopathic, usually benign tremor syndrome. Tremors of the head reported or visualized in video footage to accompany signs of dystonia in an otherwise neurologically normal dog imply dystonic head tremor and paroxysmal dyskinesia.

If the tremors are not the only sign in the patient, but are accompanied by additional neurological findings, an underlying condition should be suspected. In the presence of an underlying neurological condition, the tremor syndrome is considered as symptomatic or secondary. For example, when generalized tremors are accompanied by cerebellovestibular signs, CRTS or intoxication should be considered. When intention tremors are present along with other cerebellar signs, acerebellar disease or intoxication should be considered. When episodic head tremor manifests along with other intracranial signs, a lesion such as neoplasia or inflammation in the thalamus or/and mesencephalic aqueduct should be suspected. When tremor is present along with weakness and hyporeflexia, neuromuscular disease such as acute idiopathic polyradiculoneuritis should be considered.

3. Is the general physical examination normal?

Presence of gastrointestinal signs and hyperthermia might cause suspicion of intoxication or CRTS. Hyperthermia can be seen secondary to generalized tremors such as in case of CRTS or intoxications. Hypersalivation might be seen in cats with permethrin intoxication. Diarrhea with green or blue color can be seen in metaldehyde intoxication due to the color of the slug pellets.

4. Do the tremors get worse when the animal tries to walk or are they most severe when the animal stands?

It is important to identify when the tremors occur. If they occur only while standing but discontinue when the animal is laying down or is walking, then postural tremors should be suspected (e.g. orthostatic tremors, BIRPT, physiological tremors). If they are deteriorating while walking or doing an activity, then a kinetic tremor or twitch should be more suspected (e.g. CRTS).

5. Are the tremors continuous or episodic?

If the tremors are episodic, then idiopathic or structural episodic head tremor, dystonic head tremor (as they occur along with paroxysmal dyskinesia episodes), intention tremors (as they occur only while reaching a goal) and postural tremors (as they mainly occur while standing) should be considered. Continuous tremors are usually related with intoxication or CRTS.

6. Is the tremor progressive over time or not?

Clinical progression over time could also assist in identifying the most likely diagnosis. Remission of generalized tremors within 24-48 hours of supportive treatment without using steroids would be suggestive of intoxication over CRTS. Chronic progression of the pelvic limb tremor and expansion over other body

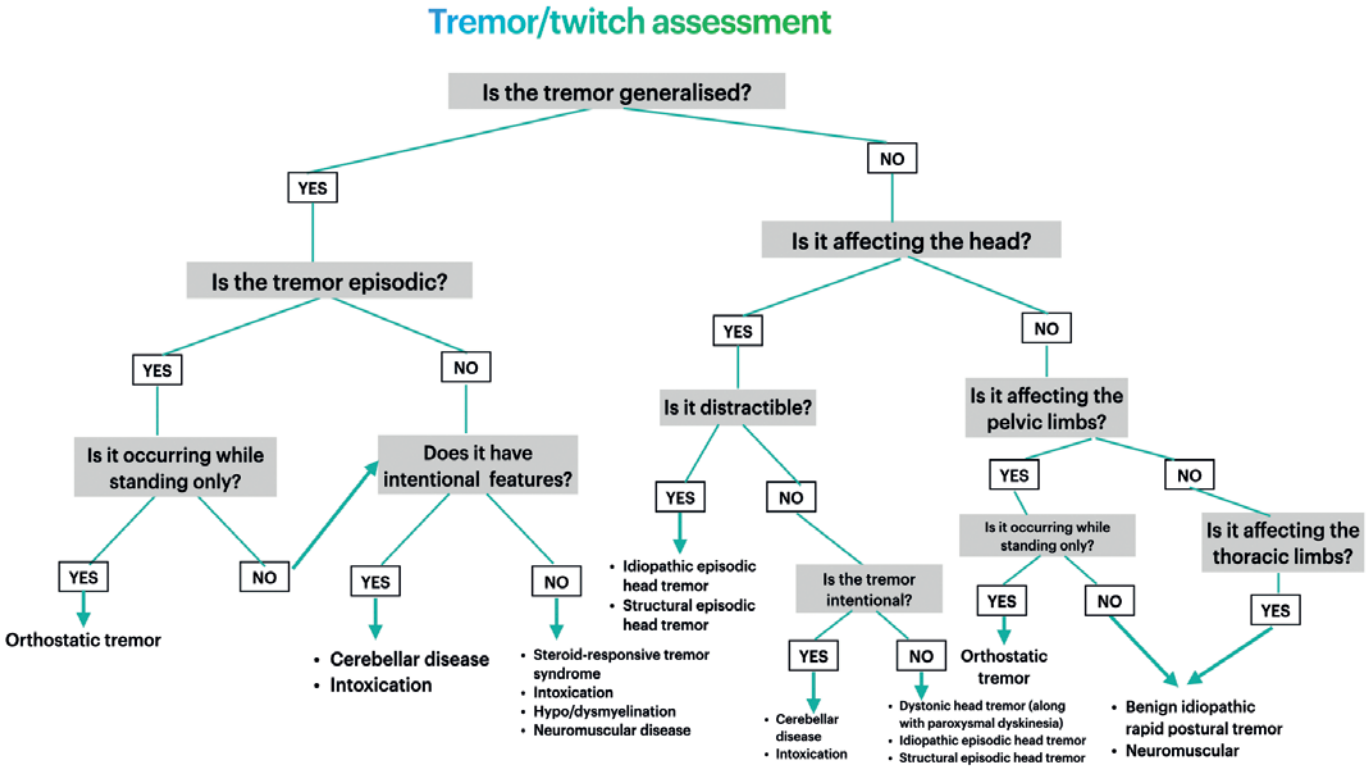

Figure 1. Diagram of clinical approach to tremors in dogs and cats.

parts is mainly seen in orthostatic tremors in contrast with other postural tremors (physiologic, BIRPT). Episodic head tremor that decreases as the dog ages might raise the suspicion of idiopathic episodic head tremor.

Trembling puppies that are improving over time (e.g. months) raise the suspicion of hypomyelinating disease (shaking puppy syndrome).

7. Is the tremor related to specific activities?

If the head tremor is elicited by reaching a goal (e.g. toy, food or water bowl), then the tremor is intentional. If the head tremor discontinues after distraction (e.g. touching the dog, calling the dog by its name, giving it a toy or treat), then idiopathic episodic head tremor is to be suspected.

8. Implementing the history within the tremor analysis (breed, age, toxic history)

It is important to implement the information from the signalment such as over-represented breeds and age (young versus old) in order to form the last version of the differential diagnosis. Thoroughly questioning the owners regarding anamnesis such as exposure of the animal to toxins or whether the dog is a scavenger, is imperative.

Advanced diagnostic tests may assist to distinguish tremors from twitches with tremors being rhythmic, or help to better define tremors, i. e. conscious electromyography (e.g. >12 Hz pathognomonic of orthostatic tremor) and identity unterlying conditions electromyography and motor nerve conduction studies under general anesthesia (e.g. for the investigation of neuromuscular disease), MRI of the brain and spinal cord (e.g. for the investigation of structural diseases).

In conclusion, tremor syndromes are variable in dogs and cats. A thorough history, clinical and neurological examination and a specific tremor assessment will help the clinician to reach a diagnosis and make an appropriate therapeutic plan. Tremor syndromes are still under-investigated in the veterinary field. More studies need to be pursued in order to improve the understanding of these syndromes and to develop effective treatment strategies.

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