

## Review

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## Classification of Involuntary Movements in Dogs: Myoclonus and Myotonia

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Myoclonus is a sudden brief, involuntary muscle jerk. Of all the movement disorders, myoclonus is the most difficult to encapsulate into any simple framework. On the one hand, a classification system is required that is clinically useful to aid in guiding diagnosis and treatment. On the other hand, there is need for a system that organizes current knowledge regarding biological mechanisms to guide scientific research. These 2 needs are distinct, making it challenging to develop a robust classification system suitable for all purposes. We attempt to classify myoclonus as “epileptic” and “nonepileptic” based on its association with epileptic seizures. Myotonia in people may be divided into 2 clinically and molecularly defined forms: (1) nondystrophic myotonias and (2) myotonic dystrophies. The former are a group of skeletal muscle channelopathies characterized by delayed skeletal muscle relaxation. Many distinct clinical phenotypes are recognized in people, the majority relating to mutations in skeletal muscle voltage-gated chloride (*CLCN1*) and sodium channel (*SCN4A*) genes. In dogs, myotonia is associated with mutations in *CLCN1*. The myotonic dystrophies are considered a multisystem clinical syndrome in people encompassing 2 clinically and molecularly defined forms designated myotonic dystrophy types 1 and 2. No mutation has been linked to veterinary muscular dystrophies. We detail veterinary examples of myotonia and attempt classification according to guidelines used in humans. This more precise categorization of myoclonus and myotonia aims to promote the search for molecular markers contributing to the phenotypic spectrum of disease. Our work aimed to assist recognition for these 2 enigmatic conditions.

**Key words:** Epilepsy; Hemifacial spasm; Pseudomyotonia; Reflex seizures.

Although ancillary aids can provide confirmation for many movement disorders, or at least eliminate diseases that may mimic the condition, the initial diagnosis rests on clinical grounds. It therefore becomes important to form a diagnosis based on inspection of a typical episode. Previous reviews have covered tremors, twitches, and paroxysmal movement disorders.<sup>1,2</sup> The purpose of this review was to give the practitioner the necessary tools to identify and distinguish myoclonus and myotonia from other involuntary movements (IM). Before embarking on such classification, it is important to realize that many of these involuntary muscle contractions can occur concurrently. For example, paroxysmal dyskinesias can have myoclonic features and some tremor syndromes may be associated with dyskinesia, myoclonus, or both.<sup>1</sup> For this reason, it is important to always consider the core movement disturbance in classification (ie, the primary involuntary contraction observed<sup>1</sup>). A comparative review of the classification and different conditions presenting with myoclonus and

### Abbreviations:

CDV	canine distemper virus
EEG	electroencephalography
EMG	electromyography
FARS	feline audiogenic reflex seizures
GTCS	generalized tonic-clonic seizures
HyperPP	hyperkalemic periodic paralysis
IM	involuntary movements
NCLs	neuronal ceroid lipofuscinosis
PAM	potassium-aggravated myotonia
PMEs	progressive myoclonic epilepsies

myotonia in people and dogs is given to raise awareness of the different manifestations of these IM.

### Myoclonus

Myoclonic movements are sudden, brief, shock-like IM. They are typically positive (caused by muscle contraction), but can sometimes be negative (due to brief loss or inhibition of muscular tonus, as in metabolic conditions caused by hepatic encephalopathy, uremic encephalopathy, or kernicterus as examples).<sup>3</sup> Myoclonic muscle contractions usually are associated with movement of the affected body part, in contrast to, for example, tremors or myokymia, where the twitches remain within the affected body segment and movement is not observed.<sup>4</sup> The following information has been obtained from the human condition, but it is suspected that a similar phenomenon occurs in animals.

### Controversies

Myoclonus is universally accepted to be a fast, involuntary muscle contraction, although opinions diverge as to what constitutes a true myoclonic movement and

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what distinguishes it from similar more rhythmic, repetitive movements such as tremors. Myoclonus may occur as part of an epileptic syndrome in which it is assumed that the myoclonic movements are epileptic in origin.<sup>5</sup> However, myoclonus may also be nonepileptic in origin and the juxtaposition of myoclonus with epileptic seizures does not imply that the 2 share the same etiology.<sup>3</sup>

A criterion for classification as myoclonic seizures is obtained by the association of myoclonic jerks and abnormal brain wave activity on electroencephalography (EEG) in people.<sup>5</sup> If this abnormal brain wave activity is persistent and results from ongoing seizures, then a diagnosis of myoclonic epilepsy may be considered. In veterinary medicine, EEG is not widely available and studies defining myoclonus based on this diagnostic tool are unavailable. Therefore, we must be cautious in defining the true nature of myoclonus in the absence of EEG.

One problem in defining myoclonus is determining whether movements clearly falling within the given definition, but not often described as myoclonic, should be considered as myoclonus or not (eg, tics, startle responses [epileptic and nonepileptic], and hemifacial spasm [see Table 1 for definitions]).<sup>4</sup> Although strictly speaking, such movements are myoclonic in nature, and some authors include these terms under the umbrella of myoclonus,<sup>3</sup> describing them as such or categorizing them as myoclonic disorders confuses, rather than clarifies, diagnostic schemes. They are considered here under the terminology of “myoclonus.” However, where the distinction is unclear, efforts are taken to highlight the differences.

### Identification

Myoclonus is best likened to the effect seen after stimulating a nerve supplying a muscle with a single electric shock (or with a train of shocks, because the myoclonic jerks can occur repetitively within the same muscle). Therefore, the keywords in identifying myoclonus are “shock-like” movements. When myoclonus occurs in series, the resulting jerks may be synchronous or moderately asynchronous. Sometimes, rhythmic

**Table 1.** Involuntary muscle contractions considered to be myoclonic in nature.

Tic	Repeated, individually recognizable, intermittent movements or movement fragments that are almost often suppressible and are usually associated with awareness of an urge to perform the movement (as such they are difficult to diagnose in the veterinary patient)
Startle	An unconscious defensive response to a sudden or threatening stimulus (eg, a noxious or auditory stimulus)
Hemifacial Spasm	Spontaneous, unilateral, irregular twitching of the muscles on one side of the face in the absence of facial nerve deficits

myoclonus can be mistaken for tremor.<sup>4</sup> The characteristic feature of the latter is that the movement is sinusoidal. Rhythmic myoclonus is more like a “square wave,” with an interval between each movement. However, tremor lacks the defining abrupt and “shock-like” character of myoclonus. Tetanus and tetany also can be difficult to distinguish on occasion although other clinical signs may prevail to determine that tetanus is present. However, appendicular movement should not be induced by tremors, tetanus, or tetany with contractions usually being more refined than those encountered with myoclonic contractions. A full description of these clinical signs can be found elsewhere.<sup>1</sup>

Ballism is a clinical sign associated with dyskinesia in people and is defined as an abrupt contraction of the limb muscles resulting in a flailing movement of the limb that is often unilateral. This movement also could be mistaken for myoclonus, but the 2 movements are distinguished by the “flailing” movement of ballismus versus the sudden “shock-like” nonpurposeful movement of myoclonus. It has not previously been reported in companion animals but its prevalence in people suggests that we remain open to its presence in veterinary species.

### Classification in People

It is suggested that the classification of myoclonus in people be approached in the same way as that of epilepsy.<sup>3</sup> In neither disorder does a single classification suffice. Both myoclonus and epilepsy can be categorized according to clinical type, etiology, pathophysiology, and perhaps even according to neuroanatomical localization or pharmacological response.<sup>6</sup> At present, there is no substantial overlap between these different classifications for either myoclonus or epilepsy, but increased understanding should improve the situation. Myoclonus is described and classified in several alternative ways in people according to distribution, etiology, anatomy, and moment of occurrence.<sup>3,4,6</sup> Whereas such efforts are not made here, it seems appropriate to review these systems for consideration as our knowledge base expands.

#### Distribution

The distribution of myoclonus can be focal, multifocal, segmental, or generalized.

#### Etiology

Myoclonus can be subdivided into physiological myoclonus (eg, hypnic jerks), essential myoclonus (idiopathic or hereditary), epileptic myoclonus, or symptomatic myoclonus. Most people are inherently familiar with myoclonus. Most of us twitch when we fall asleep and sometimes experience this twitch” as part of a dream. These episodes are entirely normal and are called hypnic jerks, but they give a good indication of what a sudden, brief, “shock-like,” involuntary movement caused by muscular contraction would feel like. Physiological myoclonus also includes hiccups. Epileptic myoclonus occurs in patients whose main complaint is one of epilepsy but who also exhibit myoclonus. This category of myoclonus is not usually associated with obvious evidence of forebrain disease initially, but with

diagnostic advancements and an increase in knowledge, it may be that many of these patients will be found to have symptomatic myoclonus.

#### *Moment of Occurrence*

In addition, careful assessment of the specific moments of occurrence for myoclonus is important. Myoclonus can occur spontaneously (at rest), but is also often present, and usually worsened, during movement (action myoclonus) or is provoked by external tactile or acoustic stimuli (reflex myoclonus).

#### *Anatomy*

The neuroanatomical basis of myoclonus is another method by which to classify this clinical sign. Accordingly, myoclonus can arise from different regions of the nervous system and is subdivided into cortical, subcortical, and peripheral types.

*Cortical myoclonus* is usually action-sensitive or stimulus-sensitive, mostly occurring in response to tactile or visual stimuli and can be seen in many forms of symptomatic myoclonus. Cortico-subcortical myoclonus is due to feedback from the cortex to other regions of the brain. Both variants may be seen on EEG because the cortex is involved.

*Subcortical myoclonus* or “brainstem” myoclonus, by contrast, is more commonly provoked by auditory stimuli and is responsible for phenomena such as hyperekplexia or startle disease. Some forms of hyperekplexia (“exaggerated surprise”) are due to mutations in genes involved in glycinergic transmission.<sup>7,8</sup> Cortical myoclonus tends to be focal, whereas subcortical myoclonus is more often generalized.

*Peripheral myoclonus* is characterized by rhythmic jerks secondary to compression or irritation of a nerve root. Hemifacial spasm is the most common example of peripheral myoclonus, whereas other causes are relatively rare.

### *Veterinary Classification*

Without knowledge regarding the intricacies of myoclonus, it seems reasonable to base veterinary classification on the occurrence or absence of generalized tonic-clonic seizures (GTCS; ie, “epileptic” and “nonepileptic” myoclonus). Future classification schemes are likely to be developed, but an effort is made here to define myoclonus according to the association of myoclonus with epilepsy.

#### *Epileptic Myoclonus (Progressive Myoclonic Epilepsies)*

When discussing veterinary diseases, myoclonus often is considered with epilepsy. Myoclonus and epilepsy may occur in certain myoclonias such as symptomatic myoclonias as part of a degenerative encephalopathy (eg, Lafora disease in dogs<sup>9</sup>) or myoclonus of unidentified etiology (eg, feline audiogenic reflex seizures [FARS]<sup>10</sup>).

The progressive myoclonic epilepsies (PMEs) are widely reported in people and are characterized by myoclonic seizures, GTCS, and progressive neurological deterioration.<sup>11</sup> In different disease entities, various types of seizures and neurological signs predominate.

Myoclonus in PME is typically fragmentary and multifocal, and often is triggered by an environmental or internal stimulus.<sup>11</sup> The age of onset, presenting signs, predominance of signs such as seizures, or myoclonus over other neurological signs vary substantially across the different disorders. There are 4 main causes of PME in people that have been more accurately defined with recent advances in genetic studies: Lafora disease, neuronal ceroid lipofuscinosis (NCLs), myoclonic epilepsy with ragged red fibers, and Unverricht-Lundborg disease.<sup>11</sup> However, few are reported in veterinary medicine with only Lafora disease<sup>9</sup> and some subtypes of the NCLs being described.

*Lafora Disease.* Lafora disease has been reported in miniature wirehaired Dachshunds,<sup>9,12</sup> Basset Hounds,<sup>13–15</sup> Beagles,<sup>16–18</sup> a Corgi,<sup>19</sup> a Miniature Poodle,<sup>14</sup> a Pointer,<sup>20</sup> and a Standard Poodle.<sup>21</sup> The disease has a late onset (range, 6–13 years; median, 7 years old) with a slowly progressive course. The myoclonic seizures often occur in response to visual and auditory stimuli and are characterized by sudden muscular twitching, from jerky head movements to generalized muscle fasciculations that may progress to GTCS. The fact that myoclonic movements occur in combination with GTCS strongly supports their designation as epileptic myoclonus.

Lafora disease (*EPM2*) in Miniature Wirehaired Dachshunds has been shown to be caused by the recessive inheritance of a biallelic expansion of a dodecamer repeat in the malin (*EPM2B* or *NHLRC1*) gene.<sup>9</sup> Mutations in the human disease also have been identified in the laforin (*EPM2A*)<sup>22</sup> and the malin (*EPM2B* or *NHLRC1*) genes.<sup>23,24</sup> These genes encode laforin starch-binding phosphatase and malin E3 ubiquitin ligase, respectively, which are postulated to prevent the accumulation of carbohydrates in neurons. A recent report documents an *EPM2B* mutation in a Beagle with myoclonic reflex seizures.<sup>25</sup>

*Neuronal Ceroid Lipofuscinosis.* The NCLs are a group of inherited PMEs resulting from lysosomal storage disorders. They typically cause myoclonic seizures, often in the terminal phase, alongside other degenerative neurological symptoms. Accumulation of autofluorescent lysosomal storage bodies in the cells of the nervous system is a characteristic feature. To date, 9 different genes have been reported in human cases of NCL,<sup>26,27</sup> 7 of which now have been described in canine NCLs: *PPT1*,<sup>28</sup> *TPPI* or *CLN2*,<sup>29</sup> *CLN5*,<sup>30,31</sup> *CLN6*,<sup>32</sup> *CLN8*,<sup>33</sup> *CTSD*,<sup>34</sup> and *ATP13A2*.<sup>35</sup> One of the canine NCL genes (*ARSG*) is now established as an excellent candidate for unsolved human NCLs.<sup>36</sup>

*Myoclonic Epilepsy of Unknown Origin.* Myoclonic epilepsy in older dogs is a not infrequent presentation to veterinary neurology clinics. Our experience in such cases is that extensive diagnostic evaluation of extra- and intracranial disease yields unremarkable results. Similar to FARS, these dogs are normal interictally in the initial stages of the disease but then slowly develop cognitive decline and neurological signs suggestive of a neurodegenerative process over several months to years.<sup>10</sup> Genetic testing has not been performed, but

some of the genetic conditions mentioned above are strong candidates for this geriatric presentation in dogs.

#### **Nonepileptic Myoclonus**

**Canine Distemper Virus.** A constant repetitive myoclonus in the absence of epileptic seizures is observed in dogs with encephalomyelitis secondary to canine distemper viral (CDV) infection. Neurological signs vary widely in dogs with CDV. The signs reflect the distribution of the virus and lesions within the central nervous system. One report suggests that one-third of dogs present with only signs of a myelopathy (ie, ataxia and paresis) in the absence of an encephalopathy.<sup>37</sup> The myoclonus often is seen affecting  $\geq 1$  limb with or without twitching of facial muscles. It is believed that the origin of the myoclonus is focal lesions causing pathological changes to the lower motor neurons of the spinal cord and cranial nerve nuclei.<sup>38</sup> This lesion creates an autonomous pacemaker resulting in these rhythmic muscle contractions. However, pathological changes are minimal in these gray matter regions suggesting a functional problem may be implicated.<sup>38</sup>

**Startle Disease.** In people, hyperekplexia (“startle” disease) is a genetic disease involving an abnormal gene for a subunit of the glycine receptor (GlyR  $\beta$  subunit, *GLRB*<sup>39</sup>) or the presynaptic glycine transporter (GlyT2; *SLC6A5*).<sup>7,8</sup> The hallmark of the disease is a triad of signs in infants including generalized stiffness, nocturnal myoclonus, and an exaggerated startle reflex. In adulthood, a pathologic startle response to minor visual, auditory, or tactile stimuli may persist.

A similar condition is reported in Irish Wolfhounds<sup>40</sup> and Labradors.<sup>41</sup> In both breeds, puppies develop extensor rigidity and a tremor around 5–7 days postpartum that is elicited by tactile stimuli, such as handling. Upon awakening or with an auditory or tactile stimulus, puppies may have a marked generalized episode of stiffening. Severe respiratory distress and cyanosis during feeding sometimes is seen, but all signs cease during sleep and when the dog is relaxed. In the reported cases, euthanasia was performed because of progression of signs, an inability to stand and difficulty feeding. Histopathology of the brain and spinal cord are normal. The mutation in Irish wolfhounds has been identified as a microdeletion in the GlyT2 gene (*SLC6A5*) with suspected autosomal recessive inheritance, consistent with reports of GlyT2 mutations in human hyperekplexia.<sup>40</sup>

**Hemifacial Spasm.** Hemifacial spasm is a chronic disorder characterized by spontaneous, unilateral, irregular twitching of the muscles on 1 side of the face in the absence of facial nerve deficits. The asynchronous frequency and “shock-like” character of hemifacial spasm distinguishes it from tremor and as such it is best classified as a myoclonus.<sup>6</sup> Usually, this segmental myoclonus lasts for relatively short periods and recurs frequently throughout the day. Hemifacial spasm is attributed to facial nerve compression near its entry zone most commonly due to the presence of an aberrant vessel compressing or encircling the nerve. The major difference between the disorder in humans and dogs is that dogs exhibit a persistent state of contraction.<sup>42</sup> In dogs,

similar clinical features of hemifacial spasm may be observed in denervation resulting from chronic facial nerve paralysis. However, these cases are distinct in that they can have facial nerve deficits (eg, an absent palpebral reflex).<sup>42</sup> Hemifacial spasm is most commonly idiopathic<sup>43–45</sup> but may occur secondary to intracranial lesions as reported in 2 dogs.<sup>42</sup> One group has suggested using the term “hemifacial tetany” given their findings of doublets on electromyography (EMG) in 2 dogs, a finding that distinguishes it from the disorder in humans.<sup>45</sup> However, given the limited number and heterogeneous nature of the reports in dogs, caution should be exercised in making conclusive judgments.

#### **Treatment**

A useful approach to the treatment of myoclonus in people is to first establish the specific type of myoclonus (cortical versus subcortical or spinal), because different drugs have efficacy in these various subclassifications of myoclonus. In general, antiepileptic drugs such as valproate, levetiracetam, and piracetam are effective in cortical myoclonus, but ineffective in other forms of myoclonus. Clonazepam may be helpful in all types of myoclonus.

From the few available studies of treating myoclonus in dogs, success appears limited. Levetiracetam appears to have some benefit in epileptic myoclonus but subcortical (eg, familial reflex myoclonus in Labradors) or spinal myoclonus (eg, CDV) appears relatively non-responsive, with clonazepam not having benefit in these conditions.<sup>37,41</sup> Recent evidence in cats indicated that levetiracetam decreased myoclonic seizure frequency by  $>50\%$  whereas phenobarbital had a negligible effect in the management of myoclonic seizures in cats with FARS.<sup>46</sup> This study strongly supports the use of levetiracetam in myoclonic seizures although currently management of epileptic myoclonus (eg, Lafora disease) in dogs with levetiracetam is based predominantly on anecdotal experience.

#### **Myotonia**

Myotonia refers to a disturbance in muscle relaxation after voluntary contraction or percussion.<sup>47</sup> It improves with continued activity. Myotonic discharges are single-fiber action potentials whose waveform is that of positive sharp waves or fibrillations. Myotonic discharges on EMG wax and wane in frequency (20–150 Hz) and amplitude (10  $\mu$ v to 1 mv), producing a characteristic “dive bomber” sound.<sup>48</sup>

#### **Controversies**

The classification of myotonic disorders has caused controversy for decades. The dispute has arisen primarily over whether myotonic dystrophy and nondystrophic myotonia should be identified as separate diseases or merely variants of the same disorder. However, other forms are identified in people and the terms dystrophic and nondystrophic myotonia seem appropriate.

### Identification

Myotonia always occurs after a voluntary movement or after a physiological or external stimulus (eg, percussion). After a period of rest, dogs develop marked stiffness in all 4 legs, exhibiting a “bunny-hopping” gait in the pelvic limbs for the first few steps that subsides with exercise but remains abnormal.<sup>49</sup> In severe cases, dogs may experience episodes of stiffening and falling sideways with all 4 limbs rigidly extended. These episodes resolve rapidly with dogs returning to ambulation but with stiffness remaining (see Video S1).

### Classification in People

Myotonia can be divided into the nondystrophic myotonias and the myotonic dystrophies.<sup>49</sup> Table 2 summarizes the different myotonic subgroups and their various clinical features.

#### Myotonic Dystrophies

In people, the myotonic dystrophies can be regarded as a multisystem clinical syndrome that encompasses 2 clinically and molecularly defined forms designated to myotonic dystrophy type 1 (DM1 also known as Steinert's disease) and myotonic dystrophy type 2 (DM2, also known as proximal myotonic myopathy), each of which is a single-gene entity.<sup>50</sup> This terminology was recommended by an international consortium and allows newly identified multisystem manifestations of this condition to be sequentially named as forms of myotonic dystrophy. Myotonic dystrophy type 1 is the most common form of adult-onset muscular dystrophy whereas DM2 tends to have a milder phenotype with later onset of signs and is rarer than DM1.

#### Nondystrophic Myotonia

The nondystrophic myotonic syndromes are caused by conventional point mutations or deletions in the genes that encode skeletal muscle chloride or sodium channels.<sup>47</sup> These include myotonia congenita, caused by mutations in the skeletal muscle chloride channel gene, *CLCN1*, and paramyotonia congenita, hyperkalemic periodic paralysis (HyperPP), and potassium-aggravated myotonia (PAM), all caused by mutations in the skeletal muscle sodium channel gene *SCN4A*.<sup>47</sup>

**Chloride Channel Myotonia.** Skeletal muscle is unusual among excitable tissues in expressing high concentrations of voltage-gated chloride channels. Mutations resulting in dysfunctional chloride channels can result in myotonia. Two forms are recognized in people: Thomsen type<sup>51</sup> and Becker type.<sup>52</sup> In both forms, muscle stiffness is most pronounced during rapid voluntary movements after a period of rest but improves with repeated activity. Thomsen type has autosomal dominant inheritance. Becker-type myotonia is recessively inherited, tends to be more severe, and more frequently is associated with muscle hypertrophy.

**Sodium Channel Myotonia.** Clinical syndromes caused by mutations in the gene encoding the alpha subunit of the skeletal muscle sodium channel (*SCN4A*) include PAM, paramyotonia congenita, and HyperPP. Numerous missense mutations have been

**Table 2.** Common myotonic disorders and their varied features.

Mutation	DM-1		DM-2	Recessive Myotonia (Becker Type)		Dominant Myotonia (Thomsen's Type)		Paramyotonia Congenita		Potassium-Aggravated Myotonia		Hyperkalemic Periodic Paralysis	
	<i>DMPK</i> (dystrophin) myotonia protein kinase)	<i>ZNF9</i> (zinc finger protein 9)		<i>CLCN-1</i> (chloride channel)	<i>CLCN-1</i> (chloride channel)	<i>SCN4A</i> (sodium channel)	<i>CLCN-1</i> (chloride channel)	<i>SCN4A</i> (sodium channel)	<i>SCN4A</i> (sodium channel)	<i>SCN4A</i> (sodium channel)	<i>SCN4A</i> (sodium channel)	<i>SCN4A</i> (sodium channel)	
Muscle atrophy	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No
Cold sensitivity	No	No	No	No	No	Yes	Yes	Possible	Possible	No	No	No	No
Muscle weakness	Yes	Yes	Yes	Common, with exercise, transient + improves rapidly	Uncommon	Common, exacerbated by cold, can be prolonged for several hours	Common, exacerbated by cold, can be prolonged for several hours	No	No	No	No	No	No
Paradoxical myotonia	None	None	None	None	None	Yes	Yes	Possible	Possible	Possible	Possible	Possible	Possible
Systemic features	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No

identified in *SCN4A* that have autosomal dominant inheritance causing altered channel properties so that the decay of sodium current is either slow (myotonia) or incomplete (weakness).<sup>47</sup>

**Paramyotonia Congenita**—Paramyotonia congenita is a rare disorder of the sodium ion channel that is transmitted through an autosomal dominant inheritance pattern in people. It is not life-threatening, and its severity usually remains stable throughout a lifetime. The onset of this disorder generally occurs between birth and early childhood. Unlike the other myotonic disorders, paramyotonia congenita has no “warm-up” effect (ie, myotonic stiffness is not decreased by continued muscle contraction). Instead, myotonic stiffness actually increases, with ongoing movement causing further disability. This phenomenon often is referred to as paradoxical myotonia.

The primary sign of paramyotonia congenita therefore is generalized myotonic stiffness. It is triggered and perpetuated by strenuous voluntary muscle activity, and may be made worse by exposure to cold temperatures. In most cases of cold-induced myotonia, stiffness can be relieved upon exposure to warm temperatures.

**Hyperkalemic Periodic Paralysis**—Hyperkalemic periodic paralysis has 3 clinically distinct manifestations: (1) without myotonia, (2) with clinical or EMG myotonia, or (3) with paramyotonia congenita. In all 3 forms, the course of the paralytic attacks is the same, with episodes of flaccid muscle weakness.<sup>53,54</sup> Episodes typically begin in the first decade of life with progression until early adulthood when the course plateaus. Sometime after midlife, episode frequency subsides substantially.<sup>53</sup> In those patients exhibiting myotonia, this sign usually diminishes with exercise, as opposed to those patients with paramyotonia in whom the muscle stiffness increases with repetitive activity.<sup>54</sup> Individuals may have normal serum potassium concentrations between attacks or even be hyperkalemic immediately after an attack because of renal excretion of potassium and reuptake of potassium by muscle.<sup>53</sup> Mutations in the *SCN4A* gene are associated with HyperPP.<sup>55</sup> It is believed that the mutant channels allow increased concentrations of sodium ions into the muscle cells which trigger the release of potassium, resulting in muscle weakness.

**Potassium-Aggravated Myotonia**—Potassium-aggravated myotonia is an autosomal dominant disease in people caused by a mutation in the *SCN4A* gene. The condition is characterized by isolated myotonia (without paralysis or other neurological deficits), induced or worsened with potassium intake, and without an increase in serum potassium concentration. In PAM, there is a gating defect of the sodium channels resulting in slow activation.<sup>56</sup> This results in an increased tendency of the muscle fibers to depolarize, which generates action potentials and myotonia.<sup>57</sup> In contrast to paramyotonia congenita, PAM does not worsen substantially after exposure to cold. It is also distinct to HyperPP in that it does not feature prominent weakness.

## Veterinary Classification

### **Nondystrophic Myotonia**

Mutations in *CLCN1* have been identified in Australian cattle dogs,<sup>58</sup> Miniature Schnauzers,<sup>59</sup> Jack Russell terrier,<sup>60</sup> and cats.<sup>61,62</sup> Mutations in *SCN4A* have yet to be identified in dogs.

**Chloride Channel Myotonia. Myotonia Congenita of the Miniature Schnauzer**—Myotonia congenita has been described in the Miniature Schnauzer and is inherited as an autosomal recessive trait sharing features of Becker-type myotonia in people. The disease results from a mutation in the skeletal muscle voltage-dependent chloride channel, *CLC-1*.<sup>59</sup> This mutation causes a shift in the voltage dependence of activation and decreases the probability of the chloride channel opening at physiologic voltages.<sup>63</sup>

Clinical signs of myotonia in affected puppies are observed at 3 weeks of age, with the first signs being an inability to rise after a period of inactivity.<sup>49</sup> As pups become able to walk, they may exhibit a stiff and stilted gait that quickly improves with activity. Sudden changes in position or posture will induce muscular stiffness. In severe cases, breathing may become affected and cyanosis may occur.<sup>49</sup> Examination can identify hypertrophy of the proximal appendicular and axial skeletal muscles. Regurgitation immediately after eating can be a problem for some dogs and may lead to aspiration pneumonia.<sup>49</sup> Investigations generally yield unremarkable results with serum creatine kinase activity remaining low. Myotonic discharges on EMG are first evident at 4 weeks of age and wax and wane with cessation within a minute of needle insertion. Histopathology of skeletal muscle is largely normal although hypertrophy of the myofibers is a common feature. Other clinical signs apparent in many affected dogs are dental and craniofacial abnormalities (eg, mandibular shortening, delayed eruption or persistence of deciduous teeth, abnormal spacing between teeth).<sup>49</sup> Prognosis in these dogs is fair provided the episodes are not so severe and frequent as to limit locomotion or cause breathing difficulties. Signs may progress or remain stable over the lifetime of the dog.<sup>49</sup>

**Myotonia Congenita of Other Breeds**—Mutations in the skeletal muscle voltage-dependent chloride channel *CLC-1* associated with myotonia congenita also have been identified in the Australian cattle dog<sup>58</sup> and Jack Russell terrier.<sup>60</sup> In both cases, only mutations in single individuals were identified and the clinical relevance of these mutations within the breed population is uncertain. The dam, sire, and the other sibling of the Jack Russell terrier were clear of the gene mutation suggesting a spontaneous mutation in the *CLC-1* gene. Similar investigations were not performed for the Australian Cattle dog. Clinical signs in both dogs resembled those reported for Miniature Schnauzers. Both the Australian Cattle dog and Jack Russell terrier were reported to have adapted to the condition well and continued to have a reasonable quality of life despite clinical signs of myotonia.

**Sodium Channel Myotonia. Paramyotonia Congenita**—A syndrome of increased stiffness with increased movement, or paradoxical myotonia, has not been reported in dogs. However, we have observed signs that resemble this disorder in a young dog although investigations were not performed (see Video S2).

**Hyperkalemic Periodic Paralysis**—A 7-month-old American Pit Bull terrier has been reported with signs similar to HyperPP.<sup>64</sup> Episodic generalized stiffness was induced by exercise and lasted 10–15 seconds. The only abnormalities detected were a mild increase in serum potassium concentration during exercise, increasing by 1 mEq/L, and a mild increase in creatine kinase activity. Provocative testing with PO administered potassium resulted in clinical signs in the absence of exercise, supporting the diagnosis of HyperPP. Genetic testing was not performed, and no similar cases in dogs have been reported. The only other veterinary species demonstrating HyperPP is in the horse, in which a mutation in the *SCN4A* gene has been identified causing muscle fasciculations and recumbence in young Quarter horses.<sup>65</sup>

**Potassium-Aggravated Myotonia**—A report of 12 cats (suspected to be related) described a muscle stiffness that was aggravated by a high potassium diet.<sup>66</sup> The clinical features included all of the components of PAM in people with the exception of evidence of myotonia on EMG. Although it is correct to suggest this condition does not share all of the similarities of PAM, it is fair to state that it is the closest description to PAM in a non-human species to date.

#### **Myotonic Dystrophy**

Myotonic dystrophy has only been reported in 4 adult dogs with clinical signs similar to those of congenital myotonia.<sup>67–69</sup> Muscle was grossly and histologically grossly abnormal, with variability in fiber size, fibrosis, rows of internal nuclei, and type I fiber atrophy. No mutation has been identified for veterinary muscular dystrophies to date.

#### **Treatment**

Treatment is not always necessary and is only indicated when the clinical signs impact on the daily life of the dog. Unfortunately, there are no effective and safe drugs available that act directly on the chloride channel. Therefore, treatment is aimed at sodium channel blockade to prevent the receptive activation of these channels and hence decrease the repetitive electrical activity of the myotonic muscle. Class I antiarrhythmic drugs such as procainamide (class 1A) and mexiletine (class 1B) affect sodium channel activation and have both been used successfully in the management of myotonia in people. In dogs, only higher doses of these medications resulted in clinical improvement, but the adverse events at these higher doses make them unsuitable as long-term treatment.<sup>70</sup>

#### **Conclusions**

Systems of classification are continually evolving. The first step in diagnosis and treatment is to identify and

classify the disorders. We provide clinical criteria for the recognition of these 2 enigmatic conditions to enable better recognition and understanding of the underlying disease mechanisms. Furthermore, we offer a classification scheme to categorize these conditions once a diagnosis has been made. “Diagnosis by inspection” is becoming a more powerful aid and should not be underestimated in the assessment of movement disorders in dogs.

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#### **References**

1. Lowrie M, Garosi L. Classification of involuntary movements in dogs: Tremors and twitches. *Vet J* 2016;214:109–116.
2. Lowrie M, Garosi L. Classification of involuntary movements in dogs: Paroxysmal dyskinesias. *Vet J* 2017;220:65–71.
3. Marsden CD, Hallett M, Fahn S. The nosology and pathophysiology of myoclonus. In: Marsden CD, Fahn S, eds. *Movement Disorders*. London: Butterworth Scientific; 1985:198–248.
4. Abdo WF, van de Warrenburg BP, Burn DJ, et al. The clinical approach to movement disorders. *Nat Rev Neurol* 2010;6:29–37.
5. Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. *Epilepsia* 2003;11:27–37.
6. Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: A practical approach for diagnosis and treatment. *Ther Adv Neurol Disord* 2011;4:47–62.
7. Rees MI, Harvey K, Pearce BR, et al. Mutations in the gene encoding GlyT2 (SLC6A5) define a presynaptic component of human startle disease. *Nat Genet* 2006;38:801–806.
8. Eulenburg V, Becker K, Gomeza J, et al. Mutations within the human GLYT2 (SLC6A5) gene associated with hyperekplexia. *Biochem Biophys Res Comm* 2006;348:400–405.
9. Lohi H, Young EJ, Fitzmaurice SN, et al. Expanded repeat in canine epilepsy. *Science* 2005;307:81.
10. Lowrie M, Bessant C, Harvey RJ, et al. Audiogenic reflex seizures in cats. *J Feline Med Surg* 2016;18:328–336.
11. Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: A review of genetic and therapeutic aspects. *Lancet Neurol* 2005;4:239–248.
12. Rusbridge C, Fitzmaurice SN, Lohi H, et al. Treatment of Lafora disease (inherited myoclonic epilepsy) in dogs. *J Vet Intern Med* 2005;19:289.
13. Kaiser E, Krauser K, Schwartz-Porsche D. Lafora’s disease (progressive myoclonus epilepsy) in the Basset Hound – Early diagnosis by muscle biopsy. *Tierarztl Prax* 1991;19:290–295.
14. Holland JM, Davis WC, Prieur DJ, et al. Lafora’s disease in the dog. A comparative study. *Am J Pathol* 1970;58:509–530.
15. Jian Z, Alley MR, Cayzer J, et al. Lafora’s disease in an epileptic Basset hound. *N Z Vet J* 1990;38:75–79.
16. Tomchick TL. Familial Lafora’s disease in the beagle dog. *Fed Proc* 1973;32:821.
17. Hegreberg GA, Padgett GA. Inherited progressive epilepsy of the dog with comparisons to Lafora’s disease of man. *Fed Proc* 1976;35:1202–1205.

18. Gredal H, Berendt M, Leifsson PS. Progressive myoclonus epilepsy in a beagle. *J Small Anim Pract* 2003;44:511–514.
19. Davis KE, Finnie JW, Hooper PT. Lafora's disease in a dog. *Aust Vet J* 1990;67:192–193.
20. Whitenack DL. Neuronal glycoproteinosis (Lafora's disease) in the dog. American Association of Veterinary Laboratory Diagnosticians, 21st Annual Proceedings, Madison, WI, 1978:493–496.
21. Cusick PK, Cameron AM, Parker AJ. Canine neuronal glycoproteinosis – Lafora's disease in the dog. *J Am Anim Hosp Assoc* 1976;12:518–521.
22. Minassian BA, Lee JR, Herbrick JA, et al. Mutations in a gene encoding a novel protein tyrosine phosphatase cause progressive myoclonus epilepsy. *Nat Genet* 1998;20:171–174.
23. Chan EM, Bulman DE, Paterson AD, et al. Genetic mapping of a new Lafora progressive myoclonus epilepsy locus (EPM2B) on 6p22. *J Med Genet* 2003;40:671–675.
24. Gómez-Abad C, Gómez-Garre P, Gutiérrez-Delgado E, et al. Lafora disease due to *EPM2B* mutations: A clinical and genetic study. *Neurology* 2005;64:982–986.
25. Hajek I, Kettner F, Simerdova V, et al. *NHLRC1* repeat expansion in two beagles with Lafora disease. *J Small Anim Pract* 2016;57:650–652.
26. Jalanko A, Braulke T. Neuronal ceroid lipofuscinoses. *Biochem Biophys Acta* 2009;1793:697–709.
27. Bras J, Verloes A, Schneider SA, et al. Mutation of the parkinsonism gene *ATP13A2* causes neuronal ceroid-lipofuscinosis. *Hum Mol Genet* 2012;21:2646–2650.
28. Sanders DN, Farias FH, Johnson GS, et al. A mutation in canine PPT1 causes early onset neuronal ceroid lipofuscinosis in a Dachshund. *Mol Genet Metab* 2010;100:349–356.
29. Awano T, Katz ML, O'Brien DP, et al. A frame shift mutation in canine TPP1 (the ortholog of human CLN2) in a juvenile Dachshund with neuronal ceroid lipofuscinosis. *Mol Genet Metab* 2006;89:254–260.
30. Melville SA, Wilson CL, Chiang CS, et al. A mutation in canine *CLN5* causes neuronal ceroid lipofuscinosis in Border collie dogs. *Genomics* 2005;86:287–294.
31. Kolicheski A, Johnson GS, O'Brien DP, et al. Australian cattle dogs with neuronal ceroid Lipofuscinosis are homozygous for a *CLN5* nonsense mutation previously identified in border collies. *J Vet Intern Med* 2016; <https://doi.org/10.1111/jvim.13971>.
32. Katz ML, Farias FH, Sanders DN, et al. A missense mutation in canine *CLN6* in an Australian shepherd with neuronal ceroid lipofuscinosis. *J Biomed Biotechnol* 2011;2011:198042.
33. Katz ML, Khan S, Awano T, et al. A mutation in the *CLN8* gene in English Setter dogs with neuronal ceroid-lipofuscinosis. *Biochem Biophys Res Comm* 2005;327:541–547.
34. Awano T, Katz ML, O'Brien DP, et al. A mutation in the cathepsin D gene (*CTSD*) in American Bulldogs with neuronal ceroid lipofuscinosis. *Mol Genet Metab* 2006;87:341–348.
35. Farias FH, Zeng R, Johnson GS. A truncating mutation in *ATP13A2* is responsible for adult-onset neuronal ceroid lipofuscinosis in Tibetan terriers. *Neurobiol Dis* 2011;42:468–474.
36. Abitbol M, Thibaud JL, Olby NJ, et al. A canine Arylsulfatase G (*ARSG*) mutation leading to a sulfatase deficiency is associated with neuronal ceroid lipofuscinosis. *Proc Natl Acad Sci USA* 2010;107:14775–14780.
37. Tipold A, Vandeveld M, Jaggy A. Neurological manifestations of canine distemper virus infection. *J Small Anim Pract* 1992;33:466–470.
38. DeLahunta A, Glass E. Upper motor neuron. In: DeLahunta A, Glass E, ed. *Veterinary Neuroanatomy and Clinical Neurology*, 3rd ed. St Louis, MO, USA: Saunders; 2009:192–220.
39. Rees MI, Lewis TM, Kwok JB, et al. Hyperekplexia associated with compound heterozygote mutations in the  $\beta$ -subunit of the human inhibitory glycine receptor (GLRB). *Hum Mol Genet* 2002;11:853–860.
40. Gill JL, Capper D, Vanbellinthen JF, et al. Startle disease in Irish wolfhounds associated with a microdeletion in the glycine transporter GlyT2 gene. *Neurobiol Dis* 2011;43:184–189.
41. Fox JG, Averill DR, Hallett M, et al. Familial reflex myoclonus in Labrador retrievers. *Am J Vet Res* 1984;45:2367–2370.
42. Van Meervenne SA, Bhatti SF, Martlé V, et al. Hemifacial spasm associated with an intracranial mass in two dogs. *J Small Anim Pract* 2008;49:472–475.
43. Roberts SR, Vainisi SJ. Hemifacial spasm in dogs. *J Am Vet Med Assoc* 1967;150:381–385.
44. Parker AJ, Cusick PK, Park RD, et al. Hemifacial spasms in a dog. *Vet Rec* 1973;93:514–516.
45. Motta L, deLahunta A. Canine hemifacial spasm: A misnomer? *J Small Anim Pract* 2015;56:480.
46. Lowrie M, Thomson S, Bessant C, et al. Levetiracetam in the management of feline audiogenic reflex seizures: A randomised, controlled, open-label study. *J Feline Med Surg* 2015; pii:1098612X15622806.
47. Matthews E, Fialho D, Tan SV, et al. The non-dystrophic myotonias: Molecular pathogenesis, diagnosis and treatment. *Brain* 2010;133:9–22.
48. Cudnon PA. Electrophysiology in neuromuscular disease. *Vet Clin North Am Small Anim Pract* 2002;32:31–62.
49. Vite CH. Myotonia and disorders of altered muscle cell membrane excitability. *Vet Clin North Am Small Anim Pract* 2002;32:169–187.
50. Turner C, Hilton-Jones D. The myotonic dystrophies: Diagnosis and management. *J Neurol Neurosurg Psychiatry* 2010;81:358–367.
51. Thomsen J. Tonische Krämpfe in willkürlich beweglichen Muskeln in Folge von ererbter psychischer disposition. *Arch Psychiatr Nervenkr* 1876;6:702–718.
52. Becker PE. *Myotonia Congenita and Syndromes Associated with Myotonia* (Topics in Human Genetics). Stuttgart: Georg Thieme Verlag; 1977.
53. Lehmann-Horn F, Jurkat-Rott K. Genotype–phenotype correlation and therapeutic rationale in hyperkalemic periodic paralysis. *Neurotherapeutics* 2007;4:216–224.
54. Charles G, Zheng C, Lehmann-Horn L, et al. Characterization of hyperkalemic periodic paralysis: A survey of genetically diagnosed individuals. *J Neurol* 2013;260:2606–2613.
55. Lehmann-Horn F, Rüdél R, Jurkat-Rott K. Nondystrophic myotonias and periodic paralyses. In: Engel A, Franzini-Armstrong C, eds. *Myology*, 3rd ed. New York, NY, USA: McGraw-Hill Professional; 2004:1257–1300.
56. Chahine M, George A Jr, Zhou M, et al. Sodium channel mutations in paramyotonia congenital uncouple inactivation from activation. *Neuron* 1994;12:281–294.
57. Lerche H, Mitrovic N, Dubowitz V, et al. Pathophysiology of paramyotonia congenita: The R1448P. *Ann Neurol* 1996;39:509–608.
58. Finnigan DF, Hanna WJ, Poma R, et al. A novel mutation of the *CLCN1* gene associated with myotonia hereditaria in an Australian cattle dog. *J Vet Intern Med* 2007;21:458–463.
59. Bhalerao DP, Rajpurohit Y, Vite CH, et al. Detection of a genetic mutation for myotonia congenita among Miniature Schnauzers and identification of a common carrier ancestor. *Am J Vet Res* 2002;63:1443–1447.
60. Lobetti RG. Myotonia congenita in a Jack Russell terrier. *J S Afr Vet Assoc* 2009;80:106–107.
61. Toll J, Cooper B, Altschul M. Congenital myotonia in 2 domestic cats. *J Vet Intern Med* 1998;12:116–119.
62. Gandolfi B, Daniel RJ, O'Brien DP, et al. A novel mutation in *CLCN1* associated with feline myotonia congenita. *PLoS ONE* 2014;30:e109926.

63. Rhodes TH, Vite CH, Giger U, et al. A missense mutation in canine CIC-1 causes recessive myotonia congenita in the dog. *FEBS Lett* 1999;456:54–58.

64. Jezyk PF. Hyperkalemic periodic paralysis in a dog. *J Am Anim Hosp Assoc* 1982;18:977.

65. Rudolph JA, Spier SJ, Byrns G, et al. Periodic paralysis in quarter horses: A sodium channel mutation disseminated by selective breeding. *Nat Genet* 1992;2:144–147.

66. Kiesewetter IS, Tipold A, Baumgärtner W, et al. Potassium-aggravated muscle stiffness in 12 cats. *J Am Vet Med Assoc* 2011;238:1026–1031.

67. Simpson ST, Braund KG. Myotonic dystrophy-like disease in a dog. *J Am Vet Med Assoc* 1985;186:495–498.

68. Smith BF, Braund KG, Steiss JE, et al. Possible adult onset myotonic dystrophy in a boxer. *J Vet Intern Med* 1998;12:120.

69. Poncelet L, Fontaine J, Balligand M. Myotonia in two aged poodles. *Vet Rec* 1991;128:599.

70. Vite CH, Cozzi F, Rich M, et al. Myotonic myopathy in a miniature Schnauzer: Case report and data suggesting abnormal

chloride conductance across the muscle membrane. *J Vet Intern Med* 1998;12:394–397.

## Supporting Information

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

**Video S1.** A mixed-breed male entire dog of unknown age re-homed from Romania with a sudden generalized muscle stiffness on movement. Video courtesy of Ed Ives.

**Video S2.** An 18-month female neutered English springer spaniel with exercise induced stiffness indicative of paramyotonia. The dog has been managed successfully by avoiding exercise and has been normal 1 year after the initial diagnosis. Video courtesy of Graham Hayes and Donald Wiggins.