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Clinical and Electrophysiological Characterization of Myokymia and Neuromyotonia in Jack Russell Terriers

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Background: Generalized myokymia and neuromyotonia (M/NM) in Jack Russell Terriers (JRTs) is related to peripheral nerve hyperexcitability syndrome in humans, a symptom complex resulting from diverse etiologies.

Objective: Clinical and electrodiagnostic evaluation is used to narrow the list of possible etiological diagnoses in JRTs with M/NM.

Animals: Nine healthy JRTs and 8 affected JRTs.

Methods: A prospective study was conducted comparing clinical and electrophysiological characteristics in 8 JRTs affected by M/NM with 9 healthy JRT controls.

Results: All affected dogs except 1 had clinical signs typical of hereditary ataxia (HA). In 6 dogs, neuromyotonic discharges were recorded during electromyogram. Motor nerve conduction studies showed an axonal neuropathy in only 1 affected dog. Compared with controls, brainstem auditory-evoked potentials (BAEP) showed prolonged latencies ($P < .05$) accompanied by the disappearance of wave components in 3 dogs. Onset latencies of tibial sensory-evoked potentials (SEP) recorded at the lumbar intervertebral level were delayed in the affected group ($P < .001$). The BAEP and SEP results of the only neuromyotonic dog without ataxia were normal.

Conclusions and Clinical Importance: The BAEP and spinal SEP abnormalities observed in JRTs with M/NM were associated with the presence of HA. Therefore, these electrophysiological findings presumably arise from the neurodegenerative changes characterizing HA and do not directly elucidate the pathogenesis of M/NM. An underlying neuronal ion channel dysfunction is thought to be the cause of M/NM in JRTs.

Key words: Dog; Electrodiagnostics; Hereditary ataxia; Potassium channels.

The clinical term myokymia describes continuous vermiform movements of the overlying skin or mucous membrane and the term neuromyotonia describes sustained generalized muscle stiffness. Both conditions are characterized by a similar electromyographic (EMG) pattern of repetitive bursts of single motor unit action potentials.[1] Neuromyotonic discharges mainly differ from myokymic discharges by their higher intraburst frequencies.[2] Because these electrophysiological phenomena do not always correlate with their analogous clinical terms, myokymic and neuromyotonic discharges need to be distinguished from clinical myokymia and neuromyotonia.[2] These terms have been used inconsistently in the literature.

Generalized myokymia and neuromyotonia (M/NM) appear to be emerging clinical phenomena in the Jack Russell Terrier (JRT) breed. In veterinary literature, M/NM has been described in 7 dogs and 1 cat.[3–5] These animals typically showed widespread vermicular subcutaneous muscular contractions and episodes of sustained generalized muscle stiffness triggered by effort or stress. During EMG, repetitive bursts of motor unit discharges were recorded. Three of the 7 described dogs were JRTs, all having an early onset of clinical signs.[4] In these JRTs, M/NM was typically seen in association with hereditary ataxia (HA).[4] A definitive cause could not be identified in any of these dogs. In addition, focal myokymia has been described in 2 dogs.[6,7]

In humans, M/NM belongs to the peripheral nerve hyperexcitability (PNH) syndrome.[8] This syndrome consists of all clinical forms of involuntary muscular contractions resulting from an excessive excitability of the peripheral nerve, including fasciculations, cramps,

Abbreviations:

BAEP	brainstem auditory-evoked potential
CDP	cord dorsum potential
CK	creatine kinase
CMAP	compound muscle action potential
EMG	electromyogram
HA	hereditary ataxia
JRT	Jack Russell Terrier
MNC	motor nerve conduction
M/NM	generalized myokymia and neuromyotonia
PNH	peripheral nerve hyperexcitability
RNS	repetitive nerve stimulation
SCA	spinocerebellar ataxia
SEP	sensory-evoked potential
WBC	white blood cell

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myokymia, and neuromyotonia. Because several causes can be responsible for PNH in humans, the aim of our study was to describe in detail the clinical and electrophysiological features in JRTs with M/NM in order to narrow the wide range of possible etiologies.

In humans, the generalized PNH syndrome usually is due to a potassium channelopathy of the peripheral nerve, either inherited in children[9] or immune-mediated in adults.[10] In these cases, additional electrodiagnostic evaluation is usually unremarkable, except for the EMG discharges.[10,11] Uncommonly, it may be a manifestation of an underlying peripheral neuropathy, in which the nerve conduction study reflects the underlying disorder.[8,12] Recently, its association with some forms of HA in humans has been recognized.[13–15] In humans with HA, brainstem auditory-evoked potential (BAEP) and sensory-evoked potential (SEP) abnormalities are common features.[16]

In this prospective study, the clinical and electrophysiological data were compared between 8 JRTs with M/NM and 9 healthy JRTs in order to direct future genetic, histopathological, and immunopathological research. This research should clarify the definitive etiological pathogenesis of M/NM in JRTs.

Material and Methods

Dogs

Eight JRTs, presented with signs of myokymia or neuromyotonia (defined as vermicular muscle twitching or muscle stiffness, respectively) affecting at least 2 different muscular regions, were prospectively investigated between 2006 and 2009 at the Neurology Department for Small Animals of Ghent University. The age of the dogs at presentation was 10 ± 6.82 months (mean $\pm$ standard deviation [SD]; range, 3.5–25 months). No patient had a history of exposure to toxins or recent medication. Nine clinically healthy and neurologically normal JRTs served as controls. The age of the controls was 6.3 ± 3.1 years (range, 1.5–10 years).

The results of clinical, laboratory, and electrophysiological data were compared between the study and the control group, with the exception of cerebrospinal fluid (CSF) analysis, which was not performed in controls. The study was conducted in accordance with the guidelines of the local Ethics Committee (reference EC 2008/025). Owners of all the dogs enrolled gave informed consent.

History and Clinical Examination

Medical histories, using a standard questionnaire (including family history), were obtained by personal communication with the owners. Each dog was fully evaluated clinically by the same investigator (A.E.V.). A CBC and serum biochemistry profile was performed in all dogs, including creatine kinase (CK), total calcium, magnesium, thyroxine, and thyroid-stimulating hormone concentrations. Serum was tested for acetylcholine receptor antibodies by immunoprecipitation radioimmunoassay.[a,17] Routine urine analysis was performed. Plasma lactate, amino acid, and carnitine concentrations were measured by enzymatic spectrophotometry,[18] ion exchange chromatography[19] and tandem mass spectrometry,[20] respectively. Urinary organic acids were quantified by gas chromatography mass spectrometry.[21] The white blood cell (WBC) count and total protein concentration in CSF were analyzed in the study group only. Cytology of CSF sediment was only performed in dogs with increased CSF WBC count, defined as >8 WBC/μL.

Electrophysiological Studies

A commercial electrophysiologic unit[b] was used for all electrodiagnostic recordings. All electrophysiological recordings were performed with the dogs under general anesthesia, except for BAEP recording, which was performed under sedation. Dogs were premedicated with dexmedetomidin[c] (20 μg/kg IV). Anesthesia was induced with propofol[d] (1.5–2 mg/kg to effect, IV) and maintained with isoflurane[e] (1–1.5%) in oxygen. Capnography and pulse oximetry were monitored. The body temperature was measured at regular intervals during each recording session. Infrared lamps or a warm waterbed was used to prevent hypothermia. In 1 dog, because of muscle artifacts during SEP recording, curarization was induced using atracurium (0.25 mg/kg IV). Train-of-four stimulation of the ulnar nerve was used to monitor the level of neuromuscular blockade. The dog was ventilated by intermittent positive pressure.

Bilateral BAEP recordings were obtained in response to click stimuli delivered through headphones at a 90 dB normal hearing level and at a stimulus rate of 10 Hz.[22] Responses to 256 stimuli were averaged and 2 subsequent recordings were performed at each side. Waves I–V were analyzed. Peak latencies, as well as interpeak latencies between peaks I–III, III–V, and I–V, were determined.

EMG, motor nerve conduction (MNC), repetitive nerve stimulation (RNS), and SEP were recorded unilaterally. Standard needle EMG recordings were made from 13 appendicular muscles of 1 side of the body (Fig 1). All other muscles of this body site, in which clinical myokymia was apparent, were also tested. Myokymic and neuromyotonic discharges were defined as spontaneous bursts of doublet, triplet, or multiplet motor unit discharges of a single or partial motor unit and distinguished by their intraburst frequency (5–150 and 150–300 Hz, respectively).[1,2]

MNC velocities and response amplitudes recorded from the cranial tibial muscles were measured after stimulation of the peroneal nerve.[23] Measurements of decremental responses in amplitude of compound muscle action potentials (CMAP) from the cranial tibial muscle to RNS at a slow stimulus rate of 3 Hz were performed in all patients and controls.[24]

SEPs were obtained after tibial nerve stimulation at the hock.[25] Recording electrodes were placed between the spinous processes of the lumbar vertebrae L4–L5 and L6–L7 as well as on the sciatic nerve at the level of the greater trochanter. Stimuli of 0.2 ms duration and 3 Hz repetition rate were used. The evoked potentials were amplified and bandpass filtered between 20 and 2 kHz. Two hundred fifty responses were averaged and 2 averages were super-

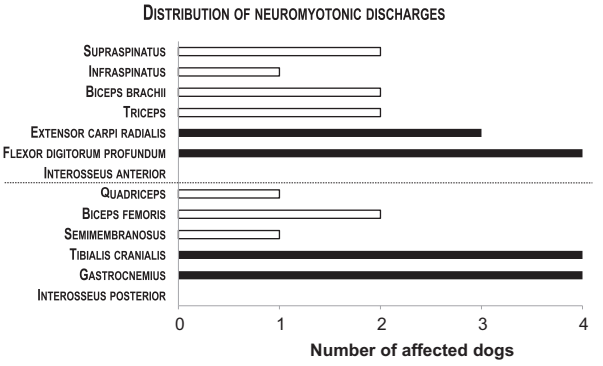

Fig 1. Electromyographic distribution of neuromyotonic discharges in Jack Russell Terriers with generalized myokymia and neuromyotonia (n = 8). Recordings were performed on 1 side of the body. A broken line separates fore- and hind limb muscles. The white and black bars represent proximal and distal limb muscles, respectively, showing that proximal and distal muscles are affected equally.

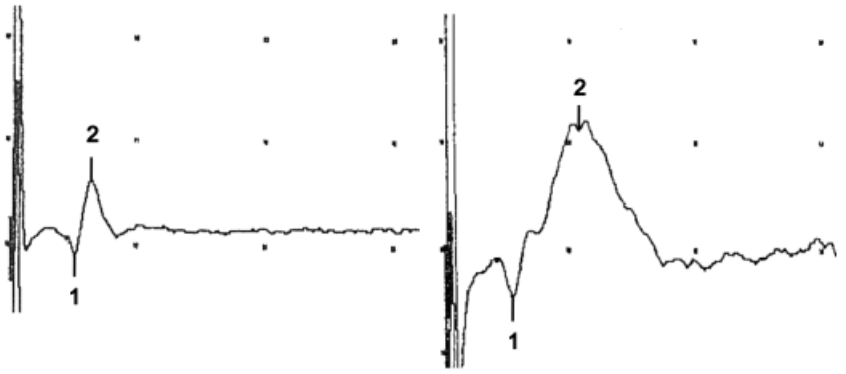

Fig 2. Tibial SEP recorded at the intervertebral level of L6–L7 (**A**) and L4–L5 (**B**) (5 μV/vertical division, 5 ms/horizontal division). The onset latency was measured from the stimulus to the initial positive (downward) deflection (peak 1). Onset-to-peak latency difference of the CDP was also analyzed (time from peak 1 to peak 2). Sensory-evoked potentials amplitudes were calculated from peak-to-peak (vertical distance between peak 1 and peak 2).

imposed. The onset latencies and peak-to-peak amplitudes of each potential were measured. Time from onset to the cord dorsum potential (CDP) peak of L4–L5 (onset-to-peak latency) was also measured.[26] Figure 2 shows the cardinal components used for SEP analysis.

Statistical Analysis

The Wilcoxon rank sum test was used to compare the 2 groups with respect to BAEP and MNC variables. The SEP onset latency and amplitude variables were compared between the 2 groups using a mixed model with dog as random effect and group, recording electrode position and their interaction as fixed effects. The SEP results were adjusted for height. Statistical analysis was performed by commercially available software.[f] Results are expressed as mean values with the SD, unless stated otherwise.

Results

Epidemiology

Male dogs (n = 6) outnumbered female dogs (n = 2) in the affected group (3 : 1). In dogs with neuromyotonic signs (n = 7), the mean age of onset was 5.5 months (range, 3–9 months). All owners reported myokymic signs to be present simultaneously or sometime before (up to several months) the onset of neuromyotonic signs. In dogs with ataxia (n = 7), subtle signs of ataxia appeared to be present at the time they were obtained by their current owner (ie, at the age of 2 months, except for 1 dog, which was purchased at the age of 4.5 months). In all of these dogs, ataxia preceded myokymic and neuromyotonic signs. Three owners reported that the ataxic gait in their dog became clearly obvious after the 1st neuromyotonic attack. One dog showed a cluster of generalized tonic-clonic seizures at the age of 11 months.

History

All affected dogs had a history of muscle twitching with or without muscle stiffness, called myokymia (n = 8) and neuromyotonia (n = 7), respectively. Exercise, excitement, or other stress triggered or exacerbated all motor features in the majority of patients (n = 7). Neuromyotonic attacks tended to occur more frequently during hot weather. Sensory manifestations, in the form of facial rubbing, were observed in 5 dogs. Hyperthermia (range, 39.4–42°C) with tachypnea and tachycardia were noted in 6 dogs during neuromyotonic attack. Vomiting or diarrhea was sporadically reported several hours after signs of skeletal muscle hyperactivity in 4 dogs. One dog developed urinary incontinence during the course of the disease.

The clinical course evolved from episodic to nearly continuous myokymia in 4 of the 8 dogs. The frequency of neuromyotonic attacks varied from occasionally to weekly. The mean duration of the attacks was between 1 and 3 hours (range, 10 minutes to 12 hours). Two dogs seemed to be in pain and vocalized during the neuromyotonic episodes.

All affected dogs had limb myokymia (n = 8). Six dogs had additional overactivity of trunk muscles (n = 2) (including thorax, abdomen, spine, neck), head muscles (n = 2) (including tongue, muzzle, eyelid), or both (n = 4). Muscle overactivity affected lower limb (n = 8) more than upper limb (n = 7) muscles. Although 2 owners reported more prominent involvement of 1 or 2 legs on the same or the opposite side, the distribution of muscular contractions appeared symmetrical and bilateral during all consultations and reevaluations.

Clinical Examination

Clinical myokymia was present in 7 of 8 patients at the time of consultation. Additionally, 2 dogs developed neuromyotonia during clinical examination. Apart from one, all affected dogs demonstrated clinical signs typical of HA, including uncoordinated and hypermetric gait. Neurologic examination identified delayed conscious proprioception in the left hind limb in 1 dog and a bilateral poor menace response in another dog.

Laboratory Investigations

Serum CK activity was mildly to moderately increased in 6 affected dogs (range, 244–1,093 IU/L; control

dogs, 186 ± 51 IU/L). Alanine transaminase (ALT) and aspartate transaminase (AST) were mildly to severely increased in 3 and 4 affected dogs, respectively (range, 55–555 and 44–4,176 IU/L; control dogs, 38.6 ± 11.41 and 32.3 ± 11.29 IU/L, respectively). Muscle enzymes were more severely increased in dogs with recent neuromyotonic attacks. All patients and controls had normal serum total calcium and magnesium concentrations. All dogs were euthyroid based on clinical and biochemical evaluation. Antiacetylcholine receptor antibody titers were normal in all dogs. Amino and organic acid screening was similar among groups. No CSF abnormalities were found in the affected group. The CSF WBC count varied between 0 and 4 WBC/μL.

Electrophysiological Investigations

The median peak and interpeak BAEP latencies are presented in Table 1. Peak latencies of all BAEP waves and interpeak latency intervals I–V were statistically longer in the affected group than in the control dogs ($P < .05$). In 3 affected dogs, there was unilateral (n = 1) or bilateral (n = 2) loss of waves III/IV and V. Latency results in the neuromyotonic dog without ataxia were normal.

The most common EMG abnormalities were doublet, triplet, and multiplet discharges of motor unit action potentials, with amplitudes varying between 100 μV and 1 mV. The auditory firing pattern was recognized as semirhythmic, meaning that bursts recurred in orderly, but not precise, intervals.[27] The interburst frequency ranged from 10 to 40 Hz (Fig 3). These repetitive bursts exhibited high intraburst frequencies (155–260 Hz), characteristic of neuromyotonic discharges. Neuromyotonic discharges were not influenced by general anesthesia, but neuromuscular blockade with atracurium performed in 1 dog abolished neuromyotonic discharges.

These neuromyotonic discharges, observed in 6 affected dogs, were usually associated with clinically visible myokymia. Only 2 of these dogs had signs of clinical neuromyotonia at the time of anesthetic induction. In these 2 dogs, bursts had a higher number of motor unit discharges (>10), a longer duration (>10 ms), and waning amplitudes, compared with the other affected dogs, apart from 1 dog, which only showed myokymia but had similar severe EMG findings. Occasional fibrillation potentials, positive sharp waves, or both were observed in distal forelimb muscles of 2 affected dogs. In 2 dogs, no neuromyotonic discharges could be recorded. In the 1st dog, clinical myokymia was not observed during consultation, but was observed at a recheck examination performed 4 months after the initial diagnostic tests. In the 2nd dog, myokymia was present at the time of consultation, but had disappeared at the time of EMG examination.

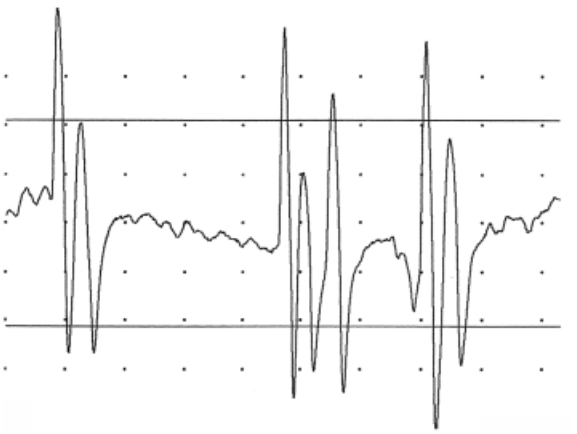

Fig 3. Neuromyotonic discharges in the form of doublets and triplets, with a high intraburst frequency of approximately 200 Hz (10 mV/vertical division, 10 ms/horizontal division).

Table 1. Results of BAEPs in JRTs (n = 8) with M/NM compared with those in healthy JRTs (n = 9).

	Latencies (ms)						
Dogs	I	II	III/IV	V	I–III	III–V	I–V
Affected							
Median	1.3*	2.25*	2.99*	3.97*	1.55	0.91	2.46*
Min.	1.13	1.94	2.66	3.56	1.50	0.77	2.16
Max.	1.60	2.51	3.45	4.19	1.88	1.43	2.96
Control							
Median	1.21	1.97	2.73	3.57	1.57	0.82	2.39
Min.	1.16	1.91	2.66	3.39	1.48	0.62	2.22
Max.	1.32	2.18	3.18	3.99	1.92	0.99	2.67

Min., minimum; max., maximum; BAEPs, brainstem auditory-evoked potentials; JRTs, Jack Russell Terriers.

Data expressed as median (minimum to maximum). In 3 affected dogs, BAEP latencies could not be recorded at 1 (n = 1) or both sites (n = 2).

*Statistically significant difference, $P < .05$.

Proximal and distal appendicular muscles were affected equally (Fig 1). In 4 patients, discharges additionally were recorded in lingual (n = 2), abdominal (n = 3), and lumbar (n = 2) muscles. The highest number of spikes per burst was noted in the tibialis cranialis, extensor carpi radialis, flexor digitorum profundus, and biceps brachii muscles.

No statistically significant differences were found in MNC velocity ($P = .20$) and amplitudes ($P = .53$) between cases and controls. However, 1 affected dog demonstrated markedly low proximal and distal CMAP amplitudes (7.6 and 5.9 mV; control values, 28.25 ± 8.88 and 26.7 ± 9.07 mV, respectively). There was no evidence of clinical relevant decremental response in CMAP amplitude during RNS in any of the dogs. An incrementing response was found in the 4 youngest affected dogs (<7 months), ranging from 7 to 25%.

The results of SEP for cases and controls are shown in Table 2. Both mean onset and peak latencies of the L6–L7 and L4–L5 SEP components were prolonged significantly in the adult patient group, consisting of all affected dogs older than 9.5 months (n = 3), compared with controls ($P < .001$). Onset-to-peak durations of the CDP were unchanged ($P = .66$). Interestingly, results of the only neuromyotonic dog without ataxia were

Table 2. Tibial nerve SEP recorded over the sciatic nerve at the greater trochanter (pSEP) and from the interspinous spaces L6–L7 and L4–L5 in JRTs with M/NM compared with those of healthy JRTs.

	pSEP		L6–L7		L4–L5		
Dogs	Onset lat. (ms)	Ampl. (μV)	Onset lat. (ms)	Ampl. (μV)	Onset lat. (ms)	Onset-peak lat. (ms)	Ampl. (μV)
Affected (n = 7)	2.45 ± 0.42	8.60 ± 5.11	3.77 ± 0.28* (n=3)	2.45 ± 5.11	4.26 ± 0.28* (n=3)	2.60 ± 0.40	7.93 ± 5.11
Control (n = 9)	1.84 ± 0.48	11.84 ± 5.07	2.75 ± 0.45	3.02 ± 5.28	3.22 ± 0.42	2.51 ± 0.36	9.23 ± 5.07

Lat., latency; ampl., amplitude; JRTs, Jack Russell Terriers; M/NM, generalized myokymia and neuromyotonia; SEP, sensory-evoked potentials.

Data expressed as mean ± SD. Latency values are height-adjusted. In 1 affected dog SEP was not performed. For SEP latency recordings of the affected group at the level of L6–L7 and L4–L5, only dogs older than 9.5 months (n = 3) were considered, because spinal cord maturation could bias SEP latency results in younger dogs.

*Statistically significant difference, $P < .05/3 = 0.0166$.

normal. Results for peripheral sensory conduction for all affected patients and control subjects were comparable ($P = .02$). The amplitudes of all responses were highly variable, although statistically similar for both groups ($P = .25$).

Family History

In Belgium, the JRT is not recognized as an official breed. Therefore, complete family data are lacking in most of the reported cases. The female sibling of one of the affected dogs also had signs of HA. Secondly, an 8-month-old female dog with HA and seizures showed maternal consanguinity with one of the dogs of the present study. In contrast, this dog had no history or signs of myokymia or neuromyotonia. A full electrodiagnostic evaluation of this dog identified BAEP and SEP abnormalities similar to those observed in the ataxic dogs with M/NM. No electrophysiological signs of myokymia or neuromyotonia were detected.

Discussion

This 1st prospective study of M/NM in JRTs documents the clinical and electrophysiological characteristics of M/NM in 8 affected dogs. The diagnosis was based on vermiform movement of the overlying skin and episodes of generalized muscular stiffness.[4,8] EMG identified characteristic repetitive bursts of motor units[1] in 6 of the affected dogs. In the 2 remaining dogs, the diagnosis was made based on typical history and the observation of clinical myokymia either at the time of presentation or during a reevaluation.

In humans, the frequent association of myokymia and neuromyotonia is believed to represent a different manifestation or degree of motor PNH.[28] Although motor nerve hyperexcitability usually predominates, the PNH syndromes also may involve sensory, autonomic, and central nervous systems.[10] In this study, >60% of the affected dogs showed intense facial rubbing, usually triggered by stress or excitement, and frequently preceding a neuromyotonic episode. This observation suggests sensory PNH.[4] Other more subtle sensory signs, such as paresthesia and numbness,[10] were possibly underdiagnosed in these dogs. Although hyperthermia, tachycardia, and tachypnea during neuromyotonic attacks might represent autonomic nerve hyperexcitability, these clinical signs could also be caused by muscle overactivity.[4,29] Similarly, vomiting and diarrhea observed occasionally after motor hyperactivity could be either a manifestation of autonomic nerve hyperexcitability or secondary to long-lasting hyperthermia. One dog in our series developed urinary incontinence during the disease. Although not previously described in JRTs with HA, this finding is probably related to the degenerative spinal changes seen in this disorder rather than to autonomic nerve hyperexcitability.[30]

Although some clinical signs are similar to those of malignant hyperthermia, none of the dogs had a history of preceding anesthesia. Only 2 humans have been reported in the medical literature with concurrent M/NM and severe hyperthermia.[29,31] Whereas M/NM has been linked to the potassium channel of the peripheral nerve, malignant hyperthermia is generally caused by a defect in the calcium-release channel of the skeletal muscle, the ryanodine receptor. Since the recent recognition of the more widespread expression of the ryanodine receptor[32] and its presumed role in motor neuron diseases,[33] a causative neuronal calcium channel disorder explaining both clinical manifestations cannot be completely ruled out, but it is considered unlikely.

Myokymia in the affected group was associated with clinical signs of HA in all but 1 dog. Gait ataxia, if present, always preceded the onset of myokymia and neuromyotonia. In a previous study of HA muscle fasciculations provoked by activity or excitement, generalized seizures and respiratory distress also were observed in several JRTs.[34] We believe that the muscle fasciculations described in this study were most probably signs of generalized myokymia.

The finding of appendicular, facial, and truncal myokymic contractions emphasizes that peripheral as well as cranial motor nerves can be hyperexcitable. Muscle overactivity affected pelvic muscles more than thoracic muscles, suggesting that nerve hyperexcitability is length dependent (ie, long nerves being the worst affected, similar to what is observed in humans).[10] Contrary to what is observed in humans,[10] distal and proximal limb muscles seemed to be equally affected in our study (Fig 1).

Hypomagnesemia and hypocalcemia were excluded as possible causes of PNH in this study.[35,36] The most

prominent biochemical finding was increased activity of muscle enzymes (AST, ALT, CK) in all but 1 affected dog. The increased activity of these enzyme activities is believed to be secondary to continuous muscular contractions, because their increase corresponded with recent neuromyotonic attacks, matching their corresponding half-life.[4] Interestingly, in none of the dogs did CSF analysis show an increase in total protein concentration, occasionally found in humans with immune-mediated neuromyotonia.[10]

BAEP results in the ataxic dogs were comparable to those of a previous study of HA in JRTs.[34] The delayed latencies of all BAEP components indicate combined degeneration of central as well as peripheral acoustic pathways, as seen in humans with HA including Friedreich's ataxia and several subtypes of spinocerebellar ataxia (SCA).[37,38] In 3 ataxic dogs, only the first 2 wave responses occurred, corresponding with the previously described predominant degenerative lesions in the cochlear nuclei, trapezoid bodies, superior olivary complex, and lateral lemnisci of the brainstem in JRTs with HA.[4,34,39] Interestingly, the single neuromyotonic dog without gait ataxia had normal BAEP latencies.

The presence of spontaneous motor unit activity in the form of semirhythmic bursts of doublet, triplet, or multiplet discharges of a single motor unit with an intraburst frequency of 155–260 Hz categorized all affected patients with EMG abnormalities (6/8) in this study as having a neuromyotonic phenotype,[2] even those in which only myokymia was observed clinically. All patients with electrophysiological evidence of PNH had visible myokymia during electrophysiological examination, of which only 2 had apparent signs of neuromyotonia just before anesthetic induction. The extent of the electrophysiological abnormality (ie, duration and amplitude of myokymic discharges) seemed to correlate with the clinical severity of muscle hyperactivity. Recordings were performed on 1 side of the body only, because no obvious differences were observed clinically between sides. In humans with M/NM, simultaneous EMG recordings of both sides are usually similar.[40]

The clinical and EMG persistence of muscle activity during general anesthesia and its disappearance after curarization with atracurium demonstrated that the generator site for the spontaneous activity is proximal to the neuromuscular junction.[41] Atracurium binds to cholinergic endplate receptors, thereby competitively inhibiting acetylcholine neurotransmitter action. In fact, local anesthetic peripheral nerve blocks in addition to curarization during EMG in human patients have been helpful in localizing the principal ectopic site of the neuromyotonic discharges in the distal portion of the peripheral nerve.[41,42] Therefore, it would be valuable to use regional anesthetics on a larger scale in JRTs with M/NM.

Most of the affected dogs (75%) had normal motor and sensory nerve conduction, suggesting that M/NM can occur in the absence of peripheral nerve damage.[10] Only 1 patient in this series had clear neurophysiological evidence of damage to motor axons. This electrophysiological abnormality is compatible with the predominant axonal changes of the peripheral nerves, detected in several JRTs affected by HA with or without M/NM.[4,34,39]

Repetitive nerve conduction was considered normal in all M/NM dogs, even though RNS showed a mild incremental response (<25%) in the youngest dogs. The latter has been described previously in young adult dogs when the cranial tibial muscle was used for CMAP recording, presumably as a result of increased synchronicity of muscle fiber discharges.[24,43] More importantly, none of the dogs had coexistent myasthenia gravis, based on the absence of decremental response during repetitive nerve conduction and confirmed by low acetylcholine receptor antibody serum titers, whereas in humans, myasthenia gravis often occurs concurrently with autoimmune PNH.[10]

Although the onset latencies of SEPs recorded at L4–L5 and L6–L7 were delayed in all ataxic dogs compared with control dogs, onset-to-peak latencies of the CDPs were similar. These abnormalities suggest dorsal nerve root (cauda equina) involvement, loss of the fastest ascending collaterals, or both, sparing the gray matter at the lumbar dorsal horn.[26] This finding is consistent with previous neuropathological descriptions of HA as a bilaterally symmetrical generalized myelopathy, characterized by Wallerian-type degeneration and spongy vacuolation affecting the white matter tracts of all funiculi, in particular the dorsolateral columns.[4,34,39] Moreover, in dorsal spinal roots, including the cauda equina, mild to extensive ballooning of the myelin sheaths has been observed.[34,39] Interestingly, the only affected dog without gait ataxia had normal latency results. Because in the present study the recorded SEP amplitudes were highly variable, as reported previously, they were considered less useful in comparing both groups.[26] A response could be recorded in each affected patient, however, in contrast to the absence of SEP responses in most patients with Friedreich's ataxia, the most common form of HA in humans.[44]

Because an important age difference existed between case and control subjects, spinal cord maturation could bias SEP results in dogs younger than 9 months. Therefore, only 3 dogs older than 9.5 months in this study were used to compare the onset latency and velocity results with those of the control group. But, if conduction velocity results of the youngest affected dogs in the present study were compared with previously established SEP values for normal young dogs,[45] all results were out of the normal range for all ataxic dogs.

The unique finding of normal BAEP and SEP results in 1 dog with M/NM without clinical signs of HA suggests that the evoked potential abnormalities in the other affected dogs showing clinical signs of HA result from the neurodegenerative changes due to HA. This assumption is supported by the fact that BAEP abnormalities have been reported previously in JRTs with HA[34] and the fact that BAEP and SEP abnormalities are a common finding in humans with HA.[16]

The association of M/NM with HA in JRTs still remains unclear. In humans, there are many causes of HA. The electrophysiological findings in this study together with the previous histopathological descriptions of HA in JRTs[4,34,39] resemble some subtypes of SCA.[38] The

subtype SCA3, also called the Machado-Joseph disease, is caused by an unstable CAG-trinucleotide expansion in the Ataxin-3 gene and has frequently been associated with fasciculations, cramps and seldom with generalized myokymia.[13–15] An experimental study showed that a defect in the ataxin-3 protein interferes with the potassium channel function.[46] Other studies demonstrated an increase in sodium conductance.[15] A similar pathomechanism indirectly affecting sodium or potassium channels is a plausible explanation for M/NM in JRTs with HA. The fact that not all M/NM dogs had HA and vice versa could possibly be attributable to the phenotypic heterogeneity of the SCA.[47] Interestingly, in another subtype (SCA2), facial myokymia is dependent on the length of trinucleotide repeats, expanding in successive generations.[48] A similar mechanism could explain the absence of M/NM in older reports of HA in JRTs.[39] Alternatively, as suggested before, M/NM may not have been recognized at the time older reports[34,39] were published.

The major limitations of this study are the age difference between the affected group and the control group, and the absence of histopathologic evidence. The 1st restriction was minimized by only comparing SEP results of the oldest affected dogs with the control group and by comparing all dogs younger than 9.5 months with previously established age-related results.[45] Although extensive histopathologic descriptions of the central and peripheral nervous system of JRTs with HA are already available in literature,[4,34,39] the lack of histopathologic correlation with the clinical and electrodiagnostic findings limits our understanding of this complex disorder. Finally, the small number of cases and controls decreases the statistical power of this study.

In conclusion, our study ruled out hypocalcemia and hypomagnesemia as possible etiologies of M/NM in JRTs. In addition, an underlying pure peripheral neuropathy was excluded. A genetic disorder that is associated with HA and that directly or indirectly affects the neuronal voltage-gated potassium or sodium channels remains as a possible cause for M/NM in JRTs. Although potassium channel antibodies were not measured (because a canine-specific test is lacking), no clinical indications for an immune-mediated potassium channelopathy were found.

Future evaluations should include fresh frozen muscle and, more importantly, peripheral nerve biopsies analyzed by a neuromuscular laboratory. However, nonspecific results are not uncommon in humans with PNH.[28] Therefore, the authors believe that, in addition, more specialized techniques such as immunohistochemistry and patch clamp of neuronal ion channels will be necessary to further elucidate the physiopathology of M/NM in JRTs with HA. Candidate screening of several genes for M/NM is in progress.

This study encourages a more extensive exploration of the use of SEP in canine neurodegenerative diseases, in particular in JRTs with HA. Meanwhile, it would be valuable to screen every JRT with HA for M/NM on the base of history, clinical, and EMG examination, because currently, there is little information about the true incidence of M/NM in dogs with HA.

Footnotes

[a] Comparative Neuromuscular Laboratory, Department of Pathology, University of California, San Francisco, CA
[b] Medelec, Sapphire 2M, Surrey, UK
[c] Dexdomitor, Orion Pharma, Esbo, Finland
[d] Propovet, Abbott Laboratories, Queensborough, Kent, UK
[e] Isoba, Schering-Plough, Brussels, Belgium
[f] SAS version 9.1, SAS Institute Inc, Cary, NC

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References

1. Phillips LH, Litchy WJ, Auger RG, et al. AAEM glossary of terms in electrodiagnostic medicine. Muscle Nerve 2001;24:S1–S49.
2. Gutmann L, Libell D, Gutmann L. When is myokymia neuromyotonia? Muscle Nerve 2001;24:151–153.
3. Reading MJ, Mckerrell RE. Suspected myokymia in a Yorkshire Terrier. Vet Rec 1993;132:587–588.
4. Van Ham L, Bhatti S, Polis I, et al. 'Continuous muscle fibre activity' in six dogs with episodic myokymia, stiffness and collapse. Vet Rec 2004;155:769–774.
5. Galano HR, Olby NJ, Howard JF, et al. Myokymia and neuromyotonia in a cat. J Am Vet Med Assoc 2005;227:1608–1612.
6. Vanhaesebrouck A, Bhatti S, Bavegems V, et al. Inspiratory stridor secondary to palatolingual myokymia in a Maltese dog. J Small Anim Pract 2010;51:173–175.
7. Walmsley GL, Smith PM, Herrtage ME, et al. Facial myokymia in a puppy. Vet Rec 2006;158:411–412.
8. Hart IK, Newsom-Davis J. Generalized peripheral nerve hyperexcitability (neuromyotonia). In: Engel A, Franzini-Armstrong C, eds. Myology, 3rd ed. New York: Mc-Graw-Hill; 2004:1301–1310.
9. Browne DL, Gancher ST, Nutt JG, et al. Episodic ataxia myokymia syndrome is associated with point mutations in the human potassium channel gene, Kcna1. Nat Genet 1994;8:136–140.
10. Hart IK, Maddison P, Newsom-Davis J, et al. Phenotypic variants of autoimmune peripheral nerve hyperexcitability. Brain 2002;125:1887–1895.
11. Imbrici P, Gualandi F, D'Adamo MC, et al. A novel KCNA1 mutation identified in an Italian family affected by episodic ataxia type 1. Neuroscience 2008;157:577–587.
12. Auger RG. AAEM minimonograph #44: Diseases associated with excess motor unit activity. Muscle Nerve 1994;17:1250–1263.
13. Franca MC Jr, D'Abreu A, Nucci A, et al. Muscle excitability abnormalities in Machado-Joseph disease. Arch Neurol 2008;65:525–529.
14. Berciano J, Infante J, Garcia A, et al. Stiff man-like syndrome and generalized myokymia in spinocerebellar ataxia type 3. Mov Disord 2006;21:1031–1035.
15. Kanai K, Kuwabara S, Arai K, et al. Muscle cramp in Machado-Joseph disease: Altered motor axonal excitability properties and mexiletine treatment. Brain 2003;126:965–973.
16. Nuwer MR, Perlman SL, Packwood JW, et al. Evoked potential abnormalities in the various inherited ataxias. Ann Neurol 1983;13:20–27.

17. Shelton GD, Cardinet GH, Lindstrom JM. Canine and human myasthenia gravis autoantibodies recognize similar regions on the acetylcholine receptor. Neurology 1988;38:1417–1423.

18. Vassault A, Bonnefont JP, Specola N, et al. Lactate, pyruvate, and ketone bodies. In: Hommes F, ed. Techniques in Diagnostic Human Biochemical Genetics: A Laboratory Manual. New York: Wiley-Liss; 1991:285–308.

19. Jones CM, Smith M, Henderson MJ. Reference data for cerebrospinal fluid and the utility of amino acid measurement for the diagnosis of inborn errors of metabolism. Ann Clin Biochem 2006;43:63–66.

20. Zytkovicz TH, Fitzgerald EF, Marsden D, et al. Tandem mass spectrometric analysis for amino, organic, and fatty acid disorders in newborn dried blood spots: A two-year summary from the New England newborn screening program. Clin Chem 2001;47: 1945–1955.

21. Duez P, Kumps A, Mardens Y. GC-MS profiling of urinary organic acids evaluated as a quantitative method. Clin Chem 1996; 42:1609–1615.

22. Sims MH, Moore RE. Auditory-evoked response in the clinically normal dog: Early latency components. Am J Vet Res 1984; 45:2019–2027.

23. Walker TL, Redding RW, Braund KG. Motor nerve conduction velocity and latency in the dog. Am J Vet Res 1979;40: 1433–1439.

24. Malik R, Ho S, Church DB. The normal response to repetitive motor-nerve stimulation in dogs. J Small Anim Pract 1989; 30:20–26.

25. Holliday TA, Weldon NE, Ealand BG. Percutaneous recording of evoked spinal cord potentials of dogs. Am J Vet Res 1979; 40:326–333.

26. Cuddon PA, Delauche AJ, Hutchison JM. Assessment of dorsal nerve root and spinal cord dorsal horn function in clinically normal dogs by determination of cord dorsum potentials. Am J Vet Res 1999;60:222–226.

27. Daube JR, Rubin DI. Needle electromyography. Muscle Nerve 2009;39:244–270.

28. Jamieson PW, Katirji MB. Idiopathic generalized myokymia. Muscle Nerve 1994;17:42–51.

29. Ashida H, Shime N, Hiramatsu N, et al. A fatal hyperthermic syndrome in a patient with myokymia. J Intensive Care Med 2001;16:243–245.

30. Tiguert R, Lewis RA, Gheiler EL, et al. Case report: Acute urinary retention secondary to Isaacs' syndrome. Neurourol Urodyn 1999;18:113–114.

31. Griffiths TD, Connolly S, Newman PK, et al. Neuromyotonia in association with malignant hyperpyrexia. J Neurol Neurosurg Psychiatry 1995;59:556–557.

32. Giannini G, Conti A, Mammarella S, et al. The ryanodine receptor/calcium channel genes are widely and differentially expressed in murine brain and peripheral tissues. J Cell Biol 1995;128: 893–904.

33. Kihira T, Utunomiya H, Kondo T. Expression of FKBP12 and ryanodine receptors (RyRs) in the spinal cord of MND patients. Amyotroph Lateral Scler Other Motor Neuron Disord 2005; 6:94–99.

34. Wessmann A, Goedde T, Fischer A, et al. Hereditary ataxia in the Jack Russell Terrier – Clinical and genetic investigations. J Vet Intern Med 2004;18:515–521.

35. Zambelis T, Licomanos D, Leonardos A, et al. Neuromyotonia in idiopathic hypoparathyroidism. Neurol Sci 2009;30:495–497.

36. Wijnberg ID, van der Kolk JH, Franssen H, et al. Electromyographic changes of motor unit activity in horses with induced hypocalcemia and hypomagnesemia. Am J Vet Res 2002;63: 849–856.

37. De Pablos C, Berciano J, Calleja J. Brain-stem auditory evoked potentials and blink reflex in Friedreich's ataxia. J Neurol 1991;238:212–216.

38. Abele M, Burk K, Andres F, et al. Autosomal dominant cerebellar ataxia type I. Nerve conduction and evoked potential studies in families with SCA1, SCA2 and SCA3. Brain 1997;120(Part 12): 2141–2148.

39. Hartley WJ, Palmer AC. Ataxia in Jack-Russell-Terriers. Acta Neuropathol 1973;26:71–74.

40. Maddison P, Mills KR, Newsom-Davis J. Clinical electrophysiological characterization of the acquired neuromyotonia phenotype of autoimmune peripheral nerve hyperexcitability. Muscle Nerve 2006;33:801–808.

41. Isaacs H. A syndrome of continuous muscle-fibre activity. J Neurol Neurosurg Psychiatry 1961;319–325.

42. Torbergsen T, Stalberg E, Brautaset NJ. Generator sites for spontaneous activity in neuromyotonia. An EMG study. Electroencephalogr Clin Neurophysiol 1996;101:69–78.

43. Godde T, Jaggy A, Vandevelde M, et al. Evaluation of repetitive nerve-stimulation in young-dogs. J Small Anim Pract 1993; 34:393–398.

44. Beltinger A, Riffel B, Stohr M. Somatosensory evoked potentials following median and tibial nerve stimulation in patients with Friedreich's ataxia. Eur Arch Psychiatry Neurol Sci 1987; 236:358–363.

45. Steiss JE, Wright JC. Maturation of spinal-evoked potentials to tibial and ulnar nerve stimulation in clinically normal dogs. Am J Vet Res 1990;51:1427–1432.

46. Jeub M, Herbst M, Spauschus A, et al. Potassium channel dysfunction and depolarized resting membrane potential in a cell model of SCA3. Exp Neurol 2006;201:182–192.

47. Cancel G, Abbas N, Stevanin G, et al. Marked phenotypic heterogeneity associated with expansion of a CAG repeat sequence at the spinocerebellar ataxia 3/Machado-Joseph disease locus. Am J Hum Gen 1995;57:809–816.

48. Jardim L, Silveira I, Pereira ML, et al. Searching for modulating effects of SCA2, SCA6 and DRPLA CAG tracts on the Machado-Joseph disease (SCA3) phenotype. Acta Neurol Scand 2003;107:211–214.