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Presumed acquired neuromyotonia of unknown cause in a cat with hyperthyroidism

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Abstract

Case summary A 16-year-old spayed female domestic shorthair cat with methimazole-treated hyperthyroidism presented with a chronic progressive history of a stiff gait progressing to recumbency. A neurological examination revealed continuous excessive muscle tone with myokymia, which exacerbated with exercise and persisted during general anaesthesia. An electromyographic study revealed myokymic discharges in all tested muscles, as well as complex repetitive discharges, fibrillation potentials and positive sharp waves. Blood tests, urinalysis and abdominal ultrasound did not reveal significant abnormalities. A histological examination of a muscle biopsy showed no specific abnormalities. A clinical diagnosis of acquired neuromyotonia with myokymia was formulated. Phenytoin treatment resulted in temporary improvement, but excessive muscle tone recurred resulting in episodes of dyspnoea. Euthanasia was elected 3 weeks after presentation.

Relevance and novel information To the best of the authors' knowledge, this is the second report of an acquired neuromyotonia in a cat. In contrast with the previous report, treatment with phenytoin resulted in only partial and temporary improvement of signs. Subsequent progression of the disease, including signs of dyspnoea and dysuria, led to the decision to euthanase the cat. In humans, acquired neuromyotonia (Isaacs syndrome) is usually due to an autoimmune response to proteins associated with voltage-gated potassium channels. More rarely, it has also been described in humans with thyroid disorders. A link with methimazole treatment or hyperthyroidism in the cat reported here could not be excluded.

Keywords: Electromyography; complex repetitive discharges; neuromyotonic discharges; myokymia; phenytoin

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Introduction

Neuromuscular disorders are fairly frequently encountered in clinical veterinary neurology.[1–4] Often, they result in fatigue, weakness, paresis and spinal hyporeflexia, but may also result in increased muscle tone.

Excessive muscle tone (severe muscle stiffness) has been reported as a clinical sign of hyperadrenocorticism in dogs ('Cushing's myotonia') and congenital myotonia in both dogs and cats.[5–8] Both these examples are suspected to be primary muscular disorders. Myokymia and neuromyotonia are clinical phenomena characterised by involuntary muscle contractions due to peripheral nerve hyperexcitability.[4,9–11] This peripheral nerve hyperexcitability may in turn have a variety of causes (eg, physical, chemical, radiation). Myokymia is

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clinically characterised by the rippling of muscles under the skin and neuromyotonia by persistent excessive muscle tone. Myokymia, the less severe presentation of peripheral nerve hyperexcitability, often progresses into neuromyotonia. During episodes of neuromyotonia, myokymia is usually visible in the affected muscles. Both are exacerbated by exercise and stress.

Congenital myotonia (myotonia congenita) has been reported in cats, with at least two different causative genetic mutations identified in the chloride voltage-gated channel 1 (*CLCN1*) gene.[5,8] Such cats exhibit excessive muscle tone early in life and may respond favourably to treatment with phenytoin. Neuromyotonia has been reported in only one cat, with clinical signs including excessive muscle tone (stiffness), myokymia and response to treatment with phenytoin.[12]

In this case report, we describe the clinical findings, electromyography (EMG) results, muscle histology findings and response to treatment with phenytoin in a 16-year-old spayed female domestic shorthair hyperthyroid cat with myokymia and neuromyotonia.

Case description

A 16-year-old spayed female domestic shorthair cat was referred for investigation of chronic progressive signs of excessive muscle tone. Six months before presentation, its owners had started to notice an unsteady gait with waxing and waning muscle stiffness. The cat had also fallen off a flight of stairs during a severe bout. Progressive deterioration was noticed during the 2 weeks before presentation. The cat had seemed uncomfortable over the previous week and was no longer able to walk more than a few steps. Attempts at walking seemed to exacerbate signs of muscle stiffness and discomfort.

Treatment initiated by the referring veterinarian included gabapentin (10 mg/kg q8h), tramadol (2 mg/kg q6–8h) and meloxicam (0.05 mg/kg q24h). The cat was treated with methimazole (0.5 mg/kg in the morning, 1.0 mg/kg in the evening) for hyperthyroidism, which had been diagnosed 3 years before. The dosage had last been changed (from 0.5 mg/kg q12h) 8 months before presentation based on a high total thyroxin (T4) during a routine checkup.

Palpation of the laryngotracheal area revealed an enlarged thyroid gland. Body condition score was 4/9, with a weight of 4.8 kg and no sign of muscle atrophy. A neurological examination yielded the following abnormalities (see Video 1 in the supplementary material):

- Posture and gait: excessive muscle tone, short-strided gait, intermittently falling in lateral recumbency with extended thoracic limbs and semi-flexed pelvic limbs, curled digits in front limbs and intermittent cervical ventroflexion with increased muscle tone in the neck.
- Postural reactions: short-strided hopping in all four limbs.
- Spinal reflexes and palpation: normal spinal reflexes, though testing was hindered by excessive muscle tone of both flexor and extensor muscles. The cat seemed uncomfortable during muscle palpation, suggesting diffuse myalgia. A full, tense bladder was palpated through equally tense abdominal muscles. Uninterrupted but incomplete voiding was elicited upon lifting with pressure on the abdomen.
- Other: percussion of the quadriceps and caudal femoral muscle groups was performed, but other than persistent excessive muscle tone, no dimple or ridge formation was noted. The skin over the pelvic limbs showed vermicular movements at rest (myokymia) that were very hard to notice because of the fur. After the neurological examination, dyspnoea was noted with a shallow, costo-abdominal breathing pattern and frequency of 50 breaths/min. No stridor was heard.

Haematology and biochemistry tests revealed no significant abnormalities aside from a slightly elevated ionised calcium level of 1.44 mmol/l (reference interval [RI] 1.13–1.38). The total T4 level was 11.0 nmol/l (RI 10.0–60.0), potassium level was 3.5 mmol/l (RI 3.5–5.8) and creatine kinase activity level was 296.0 U/l (RI 0.0–314.0). Abdominal ultrasound and urinalysis of a sample acquired by cystocentesis did not show any significant abnormalities. Urine cortisol:creatinine ratio (UCCR) was 12.1 (cortisol 136,068 pmol/l, creatinine 11,242 µmol/l). The UCCR was interpreted to be inconsistent with a diagnosis of hyperadrenocorticism.[13]

EMG was performed under general anaesthesia, during which excessive muscle tone persisted (see Video 1 in the supplementary material). The following abnormalities were found in all tested muscles, including the left-sided lumbar epaxial muscles, cranial tibial muscle, gastrocnemius muscle, biceps femoris muscle, suprascapular muscle, extensor carpi radialis muscle, triceps muscle and interosseous muscles of the pelvic and thoracic limbs: increased insertional activity; complex repetitive discharges; fibrillation potentials; positive sharp waves; myokymic discharges (bursts of multiplets) with an intraburst frequency of approximately 100 Hz and a burst frequency of 9 Hz; and long trains of complex discharges occurring infrequently, presenting as multiple repetitive motor unit action potentials with waning amplitudes that started and stopped abruptly and sometimes were triggered by needle movement, with an intraburst frequency in the range of 100–160 Hz, interpreted to be neuromyotonic discharges. Myokymic discharges were recurrent and did not seem to be associated with needle movement.

A surgical biopsy of the right cranial tibial muscle was sent for histopathological examination (see Acknowledgements). Sections were performed in transverse and longitudinal orientation and stained with haematoxylin and eosin. Epimysium and perimysium were present

with a normal amount of fibrocollagenous tissue. Intra muscular blood vessels and intramuscular nerve branches were unremarkable. Myofibre density and distribution were within normal limits. Myofibre sizes displayed mild variability in diameter, featuring few round hypertrophic fibres. Morphology and number of myonuclei were within normal limits. There was no evidence of fibre necrosis, mineralisation, sarcoplasmic vacuoles, protein inclusions or pathological storage of lipids or polysaccharides. The mitochondrial pattern was within normal limits.

Treatment with phenytoin (2.4 mg/kg q12h) was initiated. The analgesics prescribed by the referring veterinarian were continued. Methimazole dosage was lowered to 0.5 mg/kg q12h. The owners reported that the cat seemed to do better during the morning after medication was given, but deteriorated during the evening before the next dose was given. The phenytoin dosage was increased (3.6 mg/kg q12h). After some initial improvement, the cat experienced intermittent bouts of severely excessive muscle tone with dyspnoea and dysuria. Manual bladder expression was performed at the referring veterinarian to help empty the bladder. Phenytoin dosage was increased again (4.8 mg/kg q12h), with no further improvement. Euthanasia was elected owing to persistent excessive muscle tone, intermittently leading to recurrent bouts of dyspnoea. Post-mortem examination was declined.

Discussion

This is the second report of (presumed) acquired neuromyotonia in a cat. Neuromyotonia is characterised by continuous, spontaneous muscle fibre activity that persists during sleep or anaesthesia (unless neuromuscular blocking agents are employed), resulting in clinical signs of muscle stiffness (excessive muscle tone), cramps and myokymia.[4,10–12] Clinically, patients with neuromyotonia are succinctly described to 'suffer from sustained or repetitive spontaneous activity of the muscle fibres. In addition, the affected muscles stiffen and fail to relax completely following voluntary contraction. The motor activity persists during sleep, general or spinal anaesthesia, or after procaine block of the peripheral nerve.'[14,15] We discussed at length the clinical characteristics as well as the findings of the EMG examination of case and concluded that neuromyotonia best fit all the findings.

The pathophysiology of neuromyotonia involves hyperexcitability of peripheral motor nerves, which leads to the continuous stimulation of muscle fibres. Ion channel dysfunction and autoimmune mechanisms may underlie this hyperexcitability.[10,11,16] In humans, neuromyotonia can be categorised into acquired or genetic causes and may be associated with neuropathies in which nerve damage leads to increased excitability.[10,16] The acquired autoimmune variant is referred to as Isaacs syndrome.[17] This autoimmune disorder has been reported to be associated with various other disorders, including neoplasia, or medical treatments.[10,16,17] Autoantibodies have been identified in humans.[10,18]

Electrophysiologically, neuromyotonia is characterised by the presence of continuous spontaneous activity, myokymic discharges and/or neuromyotonic discharges.[4,10,11,14,15,19] Myokymic discharges are continuous or discontinuous bursts of doublets, triplets or multiplets that have an intraburst frequency in the range of 5–150 Hz.[4,10,11,14,15] Neuromyotonic discharges are infrequent, consisting of trains of complex composites of motor unit potentials with an intraburst frequency in the range of 150–300 Hz.[4,10,11,14,15] They have an abrupt onset and offset, may be triggered by needle movement and often wane in amplitude. However, it has been suggested that the distinction between myokymic and neuromyotonic discharges should be adhered to less strictly.[10,20]

Clinical signs in the only other reported feline case of acquired neuromyotonia included limb rigidity (mainly thoracic limbs), bilateral carpal flexor contracture, claw extension, muscle atrophy and myokymia (appearing as wormlike movements under the skin) in the muscles of all four limbs.[12] The presentation of that cat differed from the case we report here in that it was subacute in onset (2-week history) and less severe in development, creatine kinase activity was increased in serum samples and an excellent response to treatment with phenytoin was reported. In the case reported here, phenytoin treatment resulted in only a mild, temporary improvement of clinical signs.

The urinary dysfunction and respiratory signs reported in our case are of interest as both urinary and respiratory signs have been reported as clinical features of Isaacs syndrome in humans.[10,21] Signs of urinary dysfunction were not described in the other feline neuromyotonia case report.[12] Hyperpnoea and increased depth of respiration were reported in that case,[12] while we report hyperpnoea and a shallow breathing pattern in the present case.

It is unclear whether there is a causal relationship between the hyperthyroidism or the treatment thereof and the neuromyotonia in this case. In the human medical literature, several reports describe muscle stiffness (excessive muscle tone), increased creatine kinase activity levels, muscle cramps and myalgia secondary to thyroid disorders and thiourylene medication, such as methimazole.[22–25] Thyrotoxicosis has also been reported to result in generalised myokymia in a human case.[26] In cats, thiourylene drugs have been reported to cause autoimmune disorders, such as myasthenia gravis.[27] To our knowledge, they have not been reported to cause neuromyotonia in any species.

The limitations to this case report include a lack of more elaborate electrodiagnostic studies (eg, nerve conduction velocity studies, repetitive nerve stimulation)

and lack of a complete post-mortem examination. Nevertheless, we describe a novel clinical presentation, EMG results and muscle histology findings in only the second reported case of feline neuromyotonia.

Conclusions

Feline neuromyotonia results in excessive muscle tone worsened by exercise. It is a rarely reported disorder in cats. In the cat described here, the clinical presentation was more severe, with novel clinical signs such as dyspnoea with a shallow breathing pattern and dysuria, compared with the single previous report. A causal link between this cat's hyperthyroidism or its treatment and the neuromyotonia could not be established. A potential link would be worth investigating if similar cases arise in the future.

Supplementary material The following file is available as supplementary material:
Video 1: The cat at presentation including the electromyographic study (top window: y-axis 0.3 mV/division, x-axis 100 ms/division; bottom window: y-axis 50 µV/division, x-axis 10 ms/division).

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers, tissues and samples) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (verbal or written) for their use in the publication was obtained from the people involved.

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