Myokymia and neuromyotonia in a cat

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Myokymia and neuromyotonia represent a continuum of motor nerve axon or motor nerve terminal hyperexcitability.

Clinical signs of myokymia include undulating, vermicular, rippling, and wavelike contractions spreading across the muscle surface; neuromyotonia is characterized clinically by muscle stiffness and persistent contraction.

Phenytoin may be effective for treatment of myokymia and neuromyotonia.

A 6-year-old 2.6-kg (5.7-lb) spayed female domestic shorthair cat was referred to the North Carolina State University Veterinary Teaching Hospital with a 2-week history of rhythmic muscle movements and progressive, nonpainful contractures of both carpi. There was no history of previous illness and no history of trauma. The cat lived strictly indoors. There was 1 other cat and a dog in the household, neither of which was affected. The cat was current on vaccinations and was receiving monthly flea, tick, and heartworm preventatives. The referring veterinarian had performed a CBC and serum biochemistry panel. The only abnormalities were high creatine kinase (17,820 U/L; reference range, 56 to 529 U/L), alanine aminotransferase (140 U/L; reference range, 10 to 100 U/L), and aspartate aminotransferase (338 U/L; reference range, 10 to 100 U/L) activities. Results of tests for FeLV antigen and FIV antibody were negative, and the cat was seronegative for antibodies against Toxoplasma gondii. Serum thyroxine concentration was 2.1 µg/dL (reference range, 0.8 to 4.0 µg/dL).

A muscle biopsy specimen from the right triceps brachii muscle had been submitted by the referring veterinarian to the Comparative Neuromuscular Laboratory at the University of California; however, results of histologic examination were pending. No improvement had been seen following treatment with clindamycin (10 mg/kg [4.5 mg/lb], PO, q 12 h) for 2 weeks.

On initial examination at the veterinary teaching hospital, rectal temperature was 39.6°C (103.2°F) and heart rate was 132 beats/min. The cat appeared thin (body condition score of 4 on a scale from 1 to 9), and general health examination was unremarkable. There was 1 other cat and a dog in the household, neither of which was affected. These rhythmic muscle contractions persisted even when the cat was asleep or anesthetized. The cat was hyperpneic, with an increased depth of respiration, although no abnormalities were identified on auscultation of the lungs. Results of the remainder of the physical examination were unremarkable.

On neurological examination, the cat had normal mentation and normal cranial nerve reflexes. There was an obvious gait disturbance as a result of the abnormalities of the thoracic limbs, and proprioception was difficult to assess because of the flexed carpi. Hopping responses, however, were normal. Withdrawal reflexes were decreased in the thoracic limbs, possibly because of the generalized muscle atrophy; however, pelvic limb reflexes were normal.

The rhythmic muscle contractions were myokymic in nature, characterized by undulating, rippling, and wavelike movements across the muscle surface. The underlying lesion was localized to the lower motor neuron but could have involved any part of the lower motor neuron, including the cell body (neuronopathy), the axon (axonopathy), the neuromuscular junction (junctionopathy), and the effector organ (myopathy). The rhythmic muscle contractions were also considered to possibly be an abnormal manifestation of tetanus or a result of abnormal signaling in the gray matter of the spinal cord or an ion channel disease.

A CBC and serum biochemistry panel were performed. Abnormalities included high creatine kinase (28,380 U/L; reference range, 50 to 502 U/L) and alanine aminotransferase (195 U/L; reference range, 5 to 134 U/L) activities. Urine specific gravity was 1.070, and dipstick analysis of a urine sample obtained by means of cystocentesis revealed proteinuria (1+) and hematuria (3+). Microscopic examination of the urine sediment revealed a large number of RBCs (> 5000/hpf), rare WBCs and epithelial cells, and a few bacteria. Cardiopulmonary structures appeared normal on thoracic radiographs, and results of echocardiography and fundic examination were unremarkable.

The cat was premedicated with hydromorphone (0.05 mg/kg [0.023 mg/lb], IM) and midazolam (0.2 mg/kg [0.09 mg/lb], IM) and anesthetized with etomidate (1.4 mg/kg [0.64 mg/lb], IV) and midazolam (0.2 mg/kg, IV). Anesthesia was maintained with isoflurane. The rhythmic muscle movements persisted despite anesthesia. A CSF sample collected from the cerebellomedullary cistern was clear and colorless. Microscopic
examination of the CSF did not reveal any RBCs or WBCs; protein concentration was 7.8 mg/dL (reference range, 10 to 25 mg/dL). Cytologic examination of cytocentrifuge preparations revealed only 2 nucleated cells (1 large mononuclear cell and 1 small mononuclear cell); no pathogenic agents or atypical cells were seen.

Electromyography and nerve conduction studies were performed. Nerve conduction studies revealed normal compound muscle action potential amplitudes and normal nerve conduction velocities. Electromyography revealed spontaneous electrical activity at rest consisting of fibrillation potentials and positive sharp waves in all muscles tested, with more severe activity in muscles of the thoracic limbs. Underlying muscle necrosis was thought to explain the fibrillation potentials. Unique high-frequency discharges, identified as myokymic and neuromyotonic discharges, were also present and were more severe in the thoracic limbs. The myokymic discharges were rhythmic bursts of single motor unit potentials appearing as doublets. The neuromyotonic discharges were more prolonged bursts of nonrhythmic motor unit potentials with characteristic waning amplitudes (Figure 2).

A biopsy specimen was obtained from the biceps femoris muscle and submitted to the Comparative Neuromuscular Laboratory at the University of California. Results for this specimen and for the triceps brachii muscle specimen submitted by the referring veterinarian were similar, except that the triceps brachii muscle was more severely affected. There was variability in myofiber size with retention of a normal mosaic pattern of muscle fiber types. Intramuscular nerve branches were normal in appearance. The prominent pathologic change was the presence of numerous scattered necrotic fibers undergoing various stages of phagocytosis (Figure 3). Small numbers of basophilic regenerating fibers were also identified. No storage products were found, and there was no evidence of an inflammatory response. Findings were interpreted as a noninflammatory necrotizing myopathy with regeneration. The cause of the myonecrosis was unclear but may have resulted from the abnormal pattern of repeated muscle contractions.

The cat was initially treated with carbamazepine (10 mg/kg, PO, q 12 h) and supplemental L-carnitine (1/8 teaspoon, PO, q 8 h). However, the cat’s condition deteriorated, with persistence of the myokymia, worsening of the contracture of the carpi and extension of the thoracic limbs, and progression of the muscle atrophy evident during a recheck examination 2 weeks later. Treatment with carbamazepine was discontinued, and the cat was treated with prednisone (1 mg/kg [0.45 mg/lb], PO, q 12 h) because of the possibility that lesions were immune-mediated and the lack of response to previous treatment. Again, there was no improvement in the cat’s condition during a recheck examination 2 weeks later. The prednisone dosage was...
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Figure 3—Photomicrograph of a section of the triceps brachii muscle from the cat in Figure 1. Notice the variability in myofiber size and the scattered necrotic fibers, some of which were undergoing phagocytosis (arrows). H&E stain; bar = 90 µm.

thus slowly decreased, and treatment with phenytoin\(^d\) (3 mg/kg [1.4 mg/lb], PO, q 24 h) was initiated. Two weeks later, substantial improvement in the cat's clinical status was seen. The myokymia had resolved, contracture of the carpi had lessened, the range of motion of the thoracic limbs had increased, and ambulation had improved. Furthermore, serum creatine kinase activity had decreased (2,173 U/L; reference range, 50 to 502 U/L).

Follow-up electrodiagnostic testing 6 months after the initial examination revealed a substantial decrease in the amount of spontaneous activity in previously affected muscles. However, despite resolution of the clinically apparent rhythmic muscle contractions, the myokymic and neuromyotonic discharges were still present, albeit with a marked decrease in frequency.

A final recheck examination was performed 9 months after the initial examination; the cat was still being treated with phenytoin at this time. No myokymia was evident, and muscle mass and ambulation had returned to normal. The carpi and thoracic limbs also appeared normal. Serum creatine kinase activity was 219 U/L, serum phenytoin concentration was 30.7 µg/mL, and platelet count was 88,000/µL (reference range, 190,000 to 468,000/µL).

Myokymia and neuromyotonia are 2 clinical phenomena that represent a continuum of motor nerve axon or motor nerve terminal hyperexcitability and are distinguished by their electrophysiologic parameters.\(^1\,^7\) Myokymia is a clinical phenomenon characterized by undulating, vermicular, rippling, and wavelike movements spreading across the muscle surface.\(^1\,^8\) Facial muscles are more commonly affected than those of the extremities, and these movements persist through sleep and anesthesia.\(^1\,^3\,^8\) Myokymia is associated with a variety of disorders, including Guillain-Barré syndrome, multiple sclerosis, radiation plexopathy, brainstem tumors, and timber rattlesnake (Crotalus horridus horridus) envenomation.\(^1\,^3\,^8\)

The underlying cause of the clinical signs of myokymia is unknown, although it is suspected to involve biochemical alterations in the microenvironment of the axon membrane at any level of the motor unit.\(^1\,^3\,^8\) The resultant injury involves demyelination, radiation changes, direct toxic effects, ischemia, hypoxia, and edema.\(^1\,^3\,^8\)

Myokymic discharges arise spontaneously in the motor nerve axon where there is hyperexcitability of the axon membrane.\(^1\,^3\,^8\) This may be in the intramedullary portion of the nerve, as in individuals with multiple sclerosis, or in the peripheral portion of the nerve, as in those with Guillain-Barré syndrome.\(^1\,^3\,^8\) These myokymic discharges are short bursts of ectopically generated motor unit potentials occurring at rates of 5 to 62 Hz that appear as doublets, triplets, or multiplets.\(^1\,^3\,^8\) These bursts occur rhythmically or semirhythmically and sound like soldiers marching during electromyography.\(^1\,^3\,^8\)

Guillain-Barré syndrome typically involves bilateral facial myokymia and is associated with mild facial muscle weakness.\(^7\) It appears within the first 3 weeks of illness and typically is transient. In patients with multiple sclerosis, myokymia more commonly involves the facial muscles rather than the limb muscles, tends to be unilateral and transient, and is not associated with facial weakness.\(^8\) Clinical signs in the cat described in the present report did not fit either of these conditions, and they were therefore ruled out.

Brainstem tumors (eg, pontine gliomas, cerebellar astrocytomas, metastatic tumors, and acoustic neuromas) often produce a characteristic persistent unilateral myokymia.\(^7\) The cat described in the present report did not have other neurologic signs consistent with a brainstem tumor. Therefore, it was considered unlikely that myokymia was a result of a brainstem tumor in this cat.

Myokymia is common in human patients with radiation plexopathies, occurring in 60% to 70% of cases, but tends to be present in only one or a few muscles of the involved extremity.\(^7\) This form of myokymia usually develops decades after radiation treatments have occurred.\(^7\) The cat described in the present report had never undergone radiation therapy; therefore, radiation plexopathy was discounted as a possible cause for the myokymia.

Timber rattlesnake envenomation typically is associated with bilateral facial myokymia and myokymia of the bitten extremity as a result of hematogenous spread of the toxin.\(^8\) The myokymia tends to disappear within several hours of the patient receiving antivenin treatment. The cat in the present report lived strictly indoors and was never exposed to rattlesnakes; therefore, the myokymia was not caused by timber rattlesnake envenomation.

Neuromyotonic discharges are another type of high-frequency discharge also characterized by muscle fiber and peripheral nerve hyperexcitability. Neuromyotonic discharges are characterized by prolonged bursts of motor unit potentials occurring at rates of 150 to 300 Hz.\(^1\,^4\,^8\) These potentials begin and end abruptly, do not occur repetitively in a rhythmic fashion, and have a characteristic waning amplitude during electromyography.\(^1\,^4\,^8\) Neuromyotonic discharges may be initiated by movement, voluntary effort, or nerve stimulation.\(^3\) Neuromyotonia is characterized by muscle stiffness and
persistent contraction related to an underlying spontaneous repetitive firing of motor unit potentials. Contractions can be severe enough to produce a claw deformity of the hands; plantar flexion of the feet; enhanced spinal curvature; facial grimacing; and flexion of the elbow, wrist, hip, and knee joints.

Neuromyotonia is commonly associated with various immune-mediated disorders, including myasthenia gravis, thymoma, penicillamine induction, amyloidosis, inflammatory demyelinating polyneuropathies, and lymphoma. Recent studies now link both myokymia and neuromyotonia to antibodies directed against voltage-gated potassium channels (VGKC). More specifically, delayed rectifier potassium channels mostly involved with membrane repolarization are the channels targeted by these antibodies. When antibodies are produced against these VGKC, depolarization becomes prolonged (prolonged action potential), prompting the calcium channels to remain open longer. As a result, more calcium enters the nerve terminal and more quanta of the neurotransmitter acetylcholine are released, causing muscle hyperexcitability.

In human medicine, a radioimmunoprecipitation assay incorporating antigen solubilized from autopsied human cerebral cortical membranes in 4.5% digitonin and complexed with α-dendrotoxin labeled with iodine 125 has been used to measure serum titers of VGKC antibodies. Serum from the cat in the present report was tested with this assay, and antibodies against potassium channels were not detected. However, because feline cortical tissue was not used as the antigen, the assay was only capable of detecting cross-reacting antibodies. Similarly, in other assay systems, such as that used for detection of acetylcholine receptor antibodies, canine or feline autoantibodies may be missed if human muscle antigen is used.

To our knowledge, myokymia and neuromyotonia in a cat have not been reported previously; however, a Yorkshire Terrier suspected to have myokymia has been described, and episodic myokymia has been reported in 6 dogs. Since no underlying disease was identified, the cat described in the present report must likely have primary myokymia and neuromyotonia.

In human patients, myokymia and neuromyotonia are asymptomatic and require no treatment. However, in some patients, the condition is debilitating, warranting medical intervention. Phenytoin and, less often, carbamazepine, have proven to be effective in most human patients with myokymia and neuromyotonia. These drugs directly or indirectly reduce the flux of sodium ions during action potential generation, thus targeting the hyperexcitable state of the nerve. Phenytoin is also an anticonvulsant that inhibits voltage-gated sodium channels and depresses nerve conduction, further explaining its success in the treatment of myokymia and neuromyotonia. Other medications that have been reportedly used in human patients for treatment include sodium valproate and mexiletine. Myokymia and neuromyotonia may be linked to autoantibodies directed against VGKC; therefore, various immunosuppressive medications, including corticosteroids and azathioprine, have been used for treatment. Plasma exchange has also been quite successful in improving the clinical and electromyographic features associated with myokymia and neuromyotonia. On the other hand, IV administration of immunoglobulin has not been a successful treatment, even though it is effective in the treatment of other immune-mediated neuropathies. This is possibly a result of the direct effect of IV administration of immunoglobulin causing an increase in intracellular calcium concentration, resulting in further cramping and fasciculations. Corticosteroid treatment was unsuccessful in the cat described in the present report.

The duration of treatment in human patients with myokymia and neuromyotonia varies. Whereas some patients can be weaned from medications, others require lifelong treatment. Resolution of clinical signs is more common in patients with myokymia or neuromyotonia secondary to Guillain-Barré syndrome, multiple sclerosis, or timber rattlesnake envenomation. The myokymia associated with brainstem tumors or radiation therapy does not resolve with treatment, nor does the myokymia associated with primary autoimmune disorders.

Phenytoin has been reported to induce various hematologic reactions, including thrombocytopenia. An intermediate epoxide metabolite of phenytoin is suspected as the cause of platelet destruction, and patients should be monitored for this rare but serious adverse effect. Treatment for phenytoin-induced thrombocytopenia in humans includes discontinuation of drug administration, which typically results in rapid resolution of the thrombocytopenia; IV administration of immunoglobulin; and platelet transfusion.

In humans, the therapeutic concentration of phenytoin is close to the toxic concentration. Therapeutic concentrations of phenytoin have not been established for dogs, cats, or horses. However, the serum half-life in cats is 42 to 108 hours; therefore, high concentrations can easily be reached in this species. The cat described in the present report had a phenytoin concentration of 30.7 µg/mL at the time thrombocytopenia was identified, which is higher than the reported therapeutic range for humans (5 to 20 µg/mL). Although the thrombocytopenia did not cause observable clinical signs in this cat, the dosage of phenytoin was decreased.

References


c. Tegretol, Novartis, East Hanover, NJ.
d. Dilantin, Parke-Davis, Morris Plains, NJ.