Adult-onset motor neuron disease in three cats

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> Adult-onset, chronic, progressive, generalized weakness associated with tremors, cervical ventroflexion, dysphagia, and muscle atrophy can be associated with motor neuron disease in cats.
> Spinal reflexes are evident early but become non-detectable as motor neuron disease progresses.
> Diagnosis of motor neuron disease is supported by evidence of denervation found during examination of muscle specimens and results of electromyography that reveal fibrillation potentials with nerve conduction velocities within or only slightly less than the reference range.
> Diagnosis of motor neuron disease is confirmed histologically by detecting neuron loss and gliosis in the ventral horn of the spinal cord and consequent atrophy of ventral nerve rootlets.

A 6-year-old spayed female domestic shorthair cat (cat 1) was evaluated because of progressive weakness of the pelvic limbs, crouched gait, and tremor when walking of 1 month’s duration. Muscle twitching had been observed in the pelvic limbs when the cat was resting. Neurologic examination revealed normal mentation, cranial nerve function, conscious proprioception, and spinal reflexes. Mild muscle atrophy was evident in the caudal aspect of the thighs, and signs of discomfort were evident on palpation of all body musculature. Results of routine hematologic evaluation were unremarkable. Serum biochemical analysis revealed mildly decreased albumin concentration (2.2 g/dl; reference range, 2.5 to 3.9 g/dl). Values for creatine kinase activity were within the reference range. The cat was seropositive for FeLV on ELISA and immunofluorescent antibody testing but was seronegative for feline immunodeficiency virus. Serum IgG and IgM titers for Toxoplasma gondii were 1:512 and 0, respectively. All other cats in the household were seronegative for FeLV, feline immunodeficiency virus, and T gondii. Serum triiodothyronine concentration was 49 ng/dl (reference range, 60 to 200 ng/dl), and tetraiodothyronine concentration was 0.8 g/dl (reference range, 0.8 to 3.9 g/dl).

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Routine electromyography performed on the anesthetized cat revealed diffuse mild-to-moderate fibrillation potentials throughout the appendicular and epaxial musculature. Results for muscles of the head were considered normal. Overall motor nerve conduction velocity for the tibial nerve was 74.6 m/s (reference range for cats, 86.4 to 133.7 m/s) with 79.7 and 69.2 m/s in the proximal and distal segments, respectively. Overall motor nerve conduction velocity for the ulnar nerve (72.9 m/s) was within the reference range for cats (60.2 to 124.2 m/s). The M-wave amplitude for the proximal portion of the tibial nerve (6.5 mV) was less than the reference range for cats (9.2 to 22.3 mV). Similarly, amplitude for the distal portion of the tibial nerve (7.7 mV) was less than the reference range (15.1 to 27.4 mV), as were amplitudes for the proximal (5.2 mV; reference range, 9.5 to 24.1 mV) and distal (7.7 mV; reference range, 15.1 to 27.4) portions of the ulnar nerve. Results of repetitive nerve stimulation studies conducted at a frequency of 3 Hz were considered normal for tibial and ulnar nerves.

Biopsy specimens were collected from the gasteronemius, cranial tibial, and infraspinatus muscles. Specimens were frozen in isopentane precooled in liquid nitrogen and processed, using a standard panel of histochemical stains and enzyme reactions. Analysis of biopsy specimens revealed pathologic abnormalities consistent with active denervation. Because it was initially suspected that the neurologic disorder was related to FeLV or T gondii infection, treatment with clindamycin (50 mg/kg [23 mg/lb] of body weight, PO, for 28 days) followed by interferon (3 U, PO, q 24 h, for 30 days) was instituted.

The cat was reevaluated 4 months later. At that time, progression of muscle weakness was evident, including ventroflexion of the neck, difficulty eating, and pronounced tremors. Electrophysiologic studies were repeated, and needle electromyography revealed moderate to severe fibrillation potentials and a few complex repetitive discharges in appendicular, epaxial, facial, masticatory, and lingual musculature. Motor nerve conduction velocity for the proximal (71.4 m/s) and distal (70.8 m/s) portions of the tibial nerve and overall nerve conduction velocity for the tibial nerve (71.1 m/s) were similar to results obtained during initial examination. Overall nerve conduction velocity for the ulnar nerve (62.5 m/s) was less than during initial examination but was still within the low end of the reference range. Similar to initial examination, M-wave amplitudes for the tibial (proximal portion, 6.0 mV; distal portion, 8.5 mV) and ulnar (proximal portion, 4.0 mV; distal portion, 4.0 mV) nerves were less than the reference ranges. The owners elected to have the cat euthanatized because of the rapid progression of

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disease and lack of response to treatment. Necropsy was performed.

Gross pathologic findings were confined to a marked, diffuse loss of muscle mass. Histopathologic changes were largely confined to the CNS, although evidence of mild, subacute myocarditis and periportal hepatitis were found. The most diagnostically important and characteristic abnormalities were found in the spinal cord, with an obvious decrease in the number of neurons and gliosis in the ventral horns. Compared with samples from clinically normal cats, neuron loss was almost complete (Fig 1). Reactive astrocytes were evident, and rarified pale patches indicate sites of motor neuron depletion. Vacuolation of white matter was accompanied by a few macrophages. Ventral nerve roots were atrophic, compared with dorsal nerve roots. Scattered areas of mild spongiosis were detected in the white matter within the medulla. A protozoal cyst consistent with *T gondii* infection was detected in the gray matter of the occipital cortex but was not associated with an inflammatory response.

Muscle sections from the left triceps and left quadriceps were similar in appearance. Myofiber size was markedly varied, with some fascicles composed entirely of atrophic fibers of both fiber types, whereas other nearby fascicles were normal in size (Fig 2). Some fascicles contained singular or small groups of angular atrophied fibers. Fiber-type grouping was not observed.

In a specimen of the sciatic nerve, several myelin ovoids and areas of degenerating myelin were observed. Mild multifocal infiltrates of lymphocytes, plasma cells, and neutrophils were evident within the nerve sheath and epineurial adipose tissue. Similar changes were observed within the brachial plexus.

A 12-year-old neutered male Siamese-type cat (cat 2) was examined because of progressive weakness of the pelvic limbs and crouched gait of 2 years’ duration that became worse during the 10 days prior to examination. Neurologic examination revealed normal spinal reflexes. Fasciculations were evident on the left half of the tongue. Results of a CBC, serum biochemical analysis, and CSF analysis were within reference ranges, and the cat was seronegative for FeLV and feline infectious peritonitis virus. Electrophysiologic evaluation was not performed. Administration of dexamethasone (0.25 mg, PO, q 12 h, for 10 days) did not have an observable effect.

Reevaluation of the cat 7 months later revealed progression of muscle weakness, generalized muscle atrophy, head tremors, and bilateral tongue fasciculations. Spinal reflexes were not detected. The cat was euthanatized 17 months after initial examination, and necropsy was performed.

Specimens of brain, spinal cord with roots, peripheral nerves, and representative muscles were removed and fixed by immersion in a solution containing neutral-buffered 10% formalin. Blocks from these tissues and samples from thoracic and abdominal viscera were embedded in paraffin. Sections were cut at a thickness of 50 µm.
Three years later, the cat was reexamined because of weakness of the pelvic limbs, ataxia, head tremors, and tongue fasciculations. Other pathologic abnormalities, including a protozoal cyst in the gray matter of the occipital cortex (cat 1) and a meningioma in the falx cerebri (cat 3) were detected; however, both are common findings in older cats and often do not cause clinical signs, as in these cats.

In human beings, asymmetric and progressive fatigue, cramping, fasciculations, weakness, and atrophy of muscles are essential manifestations of ALS. Fasciculation of muscles may be the earliest manifestation of the disease. Similar abnormalities, including fasciculations of the tongue, were observed in the cats reported here. Random involvement of a few adjacent muscles may give rise to a wide variation in initial clinical syndromes. Anterior horn cells are involved in a random fashion, beginning at 1 small site and spreading in months or years to all anterior horn cells.

Figure 3—Electronmicrographs from a 12-year-old cat affected with motor neuron disease. Notice a hypertrophied astrocyte with densely arrayed intermediate filaments (A) and a swollen axon spheroid in the ventral horn containing large filamentous accumulations (B). Uranyl acetate and lead citrate stains; bar = 1 μm.

of 6 μm and stained with H&E, Luxol fast blue-cresyl violet, and silver.

Portions of the ventral horns from the caudal lumbar spinal segments were embedded in araldite resin, cut at a thickness of 1 μm, and stained with toluidine blue O and basic fuchsin. Additional sections were cut at a thickness of approximately 90 nm, stained with uranyl acetate and lead citrate, and examined at 80 kV, using an electron microscope. Light microscopy revealed marked depletion of motor neurons and prominent astrogliosis in the ventral horns of the spinal cord intimences, with degeneration and loss of axons in the ventral roots. The ventral horns also contained a large number of diffusely arranged macrophages laden with lipopigment and other debris. Vacuolated neuronal cell bodies were found in the oculomotor nucleus, and a ghost cell was detected in the facial nucleus of the brain stem. Mononuclear infiltrates were found in 1 spinal ganglion, which otherwise appeared normal. Examination of muscle specimens revealed atrophy consistent with denervation.

Electron microscopy of the ventral horns revealed hypertrophied astrocytes with densely arrayed intermediate filaments (Fig 3), swollen axons with large filamentous accumulations, and many macrophages with lipofuscin-like inclusions.

A 9-year-old neutered male domestic longhair cat (cat 3) was examined because of weakness of the pelvic limbs, ataxia, head tremors, and tongue fasciculations of 2 years' duration. Muscle tone was decreased, and generalized atrophy was evident. Spinal reflexes were normal. Results of a CBC, serum biochemical analysis, and CSF analysis were within reference ranges, and the cat was seronegative for FeLV and feline infectious peritonitis virus. Electrophysiologic evaluation was not performed. Short-term administration of dexamethasone (0.25 mg, PO, q 12 h) may have had some beneficial effect.

Three years later, the cat was reexamined because of extreme weakness. Postural reactions could not be elicited, and spinal reflexes were not detected. The cat was euthanatized, and necropsy was performed.

Similar to cats 1 and 2, cat 3 had a decrease in the number of cell bodies in the ventral horn, astrogliosis, and Wallerian degeneration in ventral roots. Similarly, a decrease in the number of cell bodies and astrogliosis were evident in the facial and oculomotor nuclei of the brain stem. Although not clinically evident, this cat also had a syncytial meningioma in the falx cerebri. Examination of muscle specimens revealed atrophy consistent with denervation.

Motor neuron disease (MND) is the term used to describe a group of disorders that have principal clinical and pathologic features related to degeneration and loss of motor neurons (neuropathies). They are distinct from demyelinating diseases of lower motor neurons, such as acute inflammatory demyelinating polyradiculoneuropathy (Landry-Guillain-Barré syndrome) in human beings or acute polyradiculoneuritis (coonhound paralysis) in dogs, which are classified as peripheral neuropathies associated with inflammation. Although well recognized in human beings and recently described in horses, adult-onset MND is rare in animals. Congenitally hereditary forms of MND (eg, spinal muscular atrophy) have been described in Rottweilers and Brittany Spaniels and in Red Danish, Brown Swiss, and Holstein-Friesian calves. Degeneration of cells in the ventral horn and neurolipofuscin accumulation also has been described in a young cat. Most MND syndromes predominantly affect lower motor neurons of the spinal cord and brain stem; however, amyotrophic lateral sclerosis (ALS), the most notable MND of human beings, may simultaneously or even preferentially affect upper motor neurons of the cerebral cortex. To our knowledge, MND in animals has been restricted to the ventral horn of the spinal cord and brain stem.

Three adult cats 5 or more years old were evaluated for progressive weakness and muscle atrophy. Necropsy revealed the cats had dramatic reductions in the number of functioning motor neurons, consistent with a diagnosis of MND. Motor neuron lesions observed in these cats were similar to those in human beings with progressive muscular atrophy, a form of ALS. In domestic animals, lower motor neuron degeneration has not been accompanied by motor cortex degeneration. Other pathologic abnormalities, including a protozoal cyst in the gray matter of the occipital cortex (cat 1) and a meningioma in the falx cerebri (cat 3) were detected; however, both are common findings in older cats and often do not cause clinical signs, as in these cats.
Profoundly atrophied muscles with adjacent normal muscles are often observed in the same extremity. Similar to this, whole atrophic muscle fascicles were adjacent to muscle fascicles containing myofibers within the reference range for size, as illustrated in muscle specimens from cat 1.

A mixture of upper and lower motor signs, including atrophic weak limbs with fasciculations and increased reflexes, is another hallmark of some forms of ALS associated with loss of corticospinal tracts (upper motor neurons) as well as lower motor neurons. This combination has not yet been recognized in domestic animals. Tendon reflexes persist until muscles become severely atrophic. Tendon reflexes were evident in all 3 cats until late in the course of the disease when hyporeflexia or areflexia were evident. Retention of reflexes in this disorder is in contrast to the hyporeflexia observed in peripheral neuropathies.

Bulbar palsy, attributable to loss of brain stem motor neurons, may be manifested by difficulty in speaking or swallowing. Examination of human patients discloses atrophy of tongue muscles and weakness of the soft palate and vocal cords. Initially, weakness may be unilateral. Unilateral tongue fasciculations were observed early in the course of the disease in cat 2, which progressed to bilateral involvement. Difficulty eating was also observed in cat 1.

Electromyography findings that support a diagnosis of MND are fibrillation potentials in muscles of the pelvic limbs as well as the thoracic limbs, reduction in the number and increase in the size of motor unit action potentials, and conduction velocities of motor nerves that are within the reference range or only slightly less than the lowest values of the reference range (ie, more than 75% of the minimal value of the reference range). Results of electromyography and nerve conduction velocity studies performed on cat 1 were consistent with these criteria. Evaluation of muscle specimens from all 3 cats confirmed denervation. Similar to human patients with ALS, results of CSF analysis were unremarkable.

Evaluation of the spinal cord in all 3 cats confirmed MND. Similar to human beings, affected horses usually have a continuum of degeneration unless they are extremely chronic cases. Early stages of degeneration are characterized by chromatolysis and cytoplasmic swelling as the cytosol becomes distended with phosphorylated neurofilaments. The nucleus swells and then fragments. This is followed by shrinkage of cell bodies and accumulation of perineuronal glial cells (satellitosis). Eventually, degenerating cells disappear as their site is replaced with reactive astrocytes, oligodendroglia, and macrophages containing lipopigment. Sometimes, eosinophilic inclusions consisting of membranous vesicles, degenerating mitochondria, and granules of endoplasmic reticulum become evident in the degenerating cytosol.

Although the cause of MND in human beings remains unknown, several possible etiologic agents have been postulated. Numerous environmental metals and organic compounds have been related to ALS. Garruto et al5 reported that a low-calcium diet and high aluminum intake resulted in pathologic changes in motor neurons of monkeys. It has also been postulated that MND is caused by a genetically controlled defect that prevents proper detoxification of environmental poisons, especially heavy metals.123 Low amounts of cycad neurotoxin (β-N-methylamino-L-alanine [BMAA]) can precipitate a slowly progressive degeneration of centrally located cells in the CNS.16 The hypothesis underlying potential cycad toxicity is that BMAA mimics glutamate, an excitatory amino acid neurotransmitter. Glutamate binds to the N-methyl-D-aspartate receptor on motor neurons; therefore, it has been proposed that BMAA may bind to that receptor and, subsequently, cause cell injury.

A viral etiologic agent has also been postulated as a cause of ALS because of similarities between ALS and poliomyelitis; however, we are not aware of any evidence that poliomyelitis virus or any other virus is the etiologic agent. One of the cats described here was infected with FeLV. Given the relatively high prevalence of FeLV infection and the rareness of MND in cats, this may be an incidental finding. The possibility that a virally induced or naturally developing immune-mediated process may underlie MND has been considered. Several antibodies have been found in the serum and nervous system of human beings with ALS, including antibodies directed against gangliosides, other glycolipids, spinal motor neurons, and purified calcium channels as well as at the node of Ranvier and motor nerve terminal.17 An animal model of immune-mediated loss of upper and lower motor neurons has been developed that uses guinea pigs, and neuropathologic characteristics of this model resemble ALS in human beings, with IgG within motor neurons and inflammatory foci of CD4+ and CD8+ T cells in ventral horn gray matter.18 It is of interest that mild multifocal infiltrates of lymphocytes, plasma cells, and neutrophils were evident within epineural adipose tissue, the brachial plexus, and muscles of cat 1. Some response to corticosteroid treatment was reported for cat 3. Mononuclear infiltrates have also been found in ganglia of horses, although their origin or importance is uncertain.

Heredity can play a major role in familial ALS in human beings, and clinical symptoms and findings are similar to those for sporadic forms of ALS.17 Differentiation is made on the basis of diagnosis of disease in other family members. The 3 cats reported here were unrelated.

Equine MND is also a model for progressive muscular atrophy. Results of studies on the pathogenesis of motor neuron degeneration in horses support an oxidative stress mechanism with an imbalance in anti- and pro-oxidant metabolites.3 Motor neuron degeneration predominates in, or is limited to, those neurons that innervate type-1 postural muscles. These have the highest oxidative requirements. The antioxidant, vitamin E, is consistently at subnormal concentrations in plasma and nervous tissues. Activity of superoxide dismutase is subnormal in RBC of these horses. Concentrations of copper and iron (pro-oxidant transition metals) are increased in these horses. The disease sporadically affects large groups of stabled horses that are not allowed to graze and that do not receive fresh, green feed. Genetic factors do not appear to be involved.
Clinical signs and results of examinations of the 3 cats reported here were consistent with a diagnosis of MND. The cause was undetermined. Owners of adult animals with progressive neuromuscular weakness, muscle atrophy, and fasciculations with retention of spinal reflexes should alert clinicians of these clinical signs. Because this disorder is slowly progressive, affected animals may survive for a considerable time if supportive care is provided by owners. This was evident in the 3 cats of our report by the large variation in survival times. Specific treatments are not currently available. As more cases are reported, the actual prevalence of MND in cats should become known, and predisposing factors can then be studied.

References


Correction: Book Review—Veterinary Laboratory Medicine: Interpretation and Diagnosis (Second Edition)

In the book review for Veterinary Laboratory Medicine: Interpretation and Diagnosis (Second Edition) (JAVMA, Feb 15, 1998, p 556), the price of the book was incorrectly listed as $145.00 instead of the correct price of $39.00. The entire listing for the book appears below.