Neuroaxonal dystrophy in a group of related cats

K. Paige Carmichael, Elizabeth W. Howerth,
John E. Oliver, Jr., Kurt Klappenbach

Abstract. A syndrome resembling previously described feline hereditary neuroaxonal dystrophy (FHND) was diagnosed in a litter of cats. The disorder was characterized by a sudden onset of hind limb ataxia that slowly progressed to hind limb paresis and paralysis. The cats were between 6 and 9 months old when clinical signs were first noted. Histologically, there was marked ballooning of axonal processes, with spheroid formation and vacuolation in specific regions of the brain and spinal cord. Some dystrophic axons contained a central periodic acid-Schiff (PAS)-positive core. Neuronal loss and gliosis were seen in certain brain stem nuclei, spinal cord nuclei, and the cerebellum. Ultrastructurally, there was hypomyelination and dysmyelination of affected axons. The PAS-positive core in dystrophic axons corresponded ultrastructurally with accumulations of electron-dense, flocculent, amorphous material. In addition, these axons contained membrane-bound osmiophilic bodies and large nonmembrane-bound vacuoles. The syndrome in this report differs from the previously described FHND in that no inner ear involvement was seen and onset of clinical signs occurred at a later age. In addition, although some of the affected cats did have diluted coat colors, abnormal coat color was not always associated with clinical disease. This disease is similar to juvenile neuroaxonal dystrophy in children and to neuroaxonal dystrophies described in horses, dogs, cattle, and sheep.

Neuroaxonal dystrophy is a degenerative neurologic disorder characterized by swelling of the distal segments of axons (spheroids) within the central nervous system. This disorder has been associated with several diseases of the nervous system in humans and in animals, including infantile neuroaxonal dystrophy (Seitelberger’s disease) and juvenile neuroaxonal dystrophy in humans, and several familial or suspected familial diseases in sheep, horses, dogs, and cats. Neuroaxonal dystrophy has also been described in several nonfamilial conditions, such as vitamin E deficiency in rats, certain intoxications, ataxia, and cystic fibrosis in children and as a natural aging change in dogs and humans. In most naturally occurring cases, the disorders were thought to be hereditary and possibly transmitted by an autosomal recessive gene. In general, however, the clinical and pathologic manifestations vary among species and among the various described syndromes.

Neuroaxonal dystrophy was previously described in 6 litters of tri-colored domestic shorthair cats. Several cats in each litter had a condition characterized by abnormal, diluted coat color and development of progressive ataxia that was first noticeable at 5-6 weeks of age. Affected cats had central nervous system lesions that closely resembled those of infantile neuroaxonal dystrophy in children. Histologically, there was accumulation of large axonal swellings in the gray matter of the brain stem. Axonal swelling was also noted in the inner ear of one affected cat. There was nerve tract degeneration in the superficial lamina of the spinal cord and optic nerves and cerebellar atrophy. Breeding experiments indicated that the disease was inherited as an autosomal recessive trait.

We have recognized another naturally occurring neurologic disease characterized by neuroaxonal dystrophy has been recognized in domestic shorthair cats. Onset of clinical signs appeared later in these cats, usually between 7 and 9 months of age, and although some of the affected cats did have a diluted coat color, abnormal coat color was not always associated with clinical disease. The objective of this report was to characterize the clinical and pathologic findings of this group of related cats and to compare these findings with the one previous report of feline neuroaxonal dystrophy.

Materials and methods

Case history. A 3-yr-old female faded calico domestic shorthair barn cat was submitted to the Athens Diagnostic Laboratory for necropsy examination. The cat had a history of hind limb ataxia that had slowly progressed to hind limb paresis and paralysis. The cat was from a litter of 5 cats in which 1 littermate, a gray male, had developed similar clinical signs when he was 9-10 mo old. Histologic examination of the brain of the faded calico female showed changes typical of neuroaxonal dystrophy.

Three related male cats were donated to the University of Georgia Teaching Hospital in an effort to further characterize
this condition. Two of these were littermates and born to the same queen as the affected gray and faded calico cats. They were approximately 1.5 years old and were the only 2 cats affected in a litter of four. Reportedly, clinical signs of hind limb ataxia were first noted between 6 and 9 mo of age. One of the cats was faded orange (O1) and the other was black (B1). The third donated cat was the offspring of the faded calico cat. He was solid black (B2), approximately 9 months old, and clinically normal.

**Clinical examination.** Each cat had a complete physical examination upon admission. Blood, serum, and urine samples were collected for a complete blood count (CBC), serum chemistries, feline leukemia virus and feline immunodeficiency virus testing, toxoplasma titers, and urinalysis. A complete neurologic examination was also conducted. The animals were anesthetized, and electrodiagnostic tests consisting of electromyography, motor and sensory nerve conduction velocities, repetitive stimulation for assessment of decremental response, F-wave analysis, brain stem auditory evoked response, and electroencephalograms were performed.

**Pathology.** Gross necropsy examinations were performed immediately after the cats were euthanized with barbiturate overdose. Brain, spinal cord, skeletal muscle, brachial and sciatic nerves, eyes, inner ear, skin, and thoracic and abdominal visceral organs were collected from each cat. One cat (O1) was perfusion fixed with 10% neutral buffered formalin following saline infusion. Tissues from the other 2 cats were immersion fixed in 10% formalin. Tissues were embedded in paraffin, and 5-µm sections were cut and stained with hematoxylin and eosin (HE). Selected sections were stained with Bodian’s silver stain, Luxol fast blue-cresyl violet, periodic acid-Schiff (PAS), Fite-Faracco acid-fast stain, and Congo red. Sections of the lateral cuneate nucleus of O1 were immediately postfixed in a solution containing 2% glutaraldehyde, 2% paraformaldehyde, and 0.2% picric acid in 0.1 M cacodylate buffer and processed routinely for electron microscopic examination.

**Results**

**Clinical examination.** All 3 cats had varying degrees of hind limb paresis and ataxia ranging from severe (crouched standing position with reluctance to move and a crouched, dragging, rolling gait when forced to move) in the older cats to minimal in the younger cat (B2). Bilateral hind limb muscle atrophy was noted in O1 and B1. The 2 older cats (O1 and B1) had severe proprioceptive deficits in both hind limbs. The marked hind limb paresis in the older cats became progressively worse over a 2-month period. All cats had a mild conjunctivitis that responded well to oral tetracycline.

CBC, biochemistries, and urinalyses of all 3 cats were unremarkable. All cats were serologically negative for antibody to feline leukemia and feline immunodeficiency virus. One cat (O1) had an IgG titer of 1:256 and an IgM titer of 1:512 to *Toxoplasma gondii*, indicating recent exposure. The electrodiagnostic tests showed no peripheral nerve or muscle abnormalities.

**Pathology.** Grossly, 2 of the cats (O1 and B1) had mild atrophy of the semimembranosus and semitendinosus muscles. Microscopically, cats O1 and B1 had significant histopathologic changes in the brain and spinal cord. In general, lesions were confined to nerve tracts and brain stem nuclei associated with sensory perception and proprioception. These lesions were bilateral and symmetrical and most severe in the lateral cuneate nucleus, medial cuneate nucleus, and nucleus gracilis in the brain stem. These nuclei had marked neuronal depletion with accumulation of large numbers of spheroids (Fig. 1) that ranged in size from small (8 µm in diameter) to large (100 µm in diameter). These structures occasionally were torpedo shaped or irregularly shaped and in longitudinal section appeared as swollen eosinophilic, homogeneous spheroids with terminal ballooning when stained with HE. Occasionally, they stained lightly basophilic or appeared slightly granular. Many spheroids had a central dense, eosinophilic core that stained brightly PAS-positive. Many of the spheroids contained 1 to several vacuoles of various sizes (6-20 µm in diameter). The adjacent neuropil was also very vacuolated, with vacuoles ranging in size from 25 to 100 µm in diameter. These vacuoles were often multicompartmental. There was often gliosis with accumulations of microglia in glial nodules in affected nuclei and around small blood vessels.

There was loss of Purkinje cells in the cerebellar cortex (Fig. 2), especially in the vermis. Occasional Purkinje cells were swollen and degenerating. Many spheroids were in the granular layer of the cerebellar cortex. The white matter of the cerebellum had multifocal areas of vacuolation. The cerebellar nuclei had changes similar to those seen in the brain stem nuclei.

There was severe bilateral vacuolization in ascending and descending nerve tracts in the white matter of the cervical, thoracic, and lumbar spinal cord. In the cervical spinal cord, these changes were most severe in the fasciculus gracilis (Fig. 3) and the fasciculus cuneatus. Vacuoles ranged in size from 10 to 150 µm in diameter. A few vacuoles contained accumulations of pigment. Spheroids ranging in size from 8 to 35 µm in diameter were also seen in these tracts. Mild gliosis and perivascular lymphocytic cuffing were noted, especially around blood vessels. Vacuolization and spheroid formation were also bilateral in the dorsolateral funiculus of the spinal cord in the area of the dorsal spinocerebellar tract. These changes were not as severe as those in the fasciculus gracilis and the fasciculus cuneatus. In the caudal thoracic spinal cord and the lumbar spinal cord, vacuolation and spheroid formation were seen in the ventral and ventromedial funiculi. The nucleus thoracis in the gray matter of the spinal cord had changes similar to those seen in the brain stem and cerebellar nuclei.
No histologic abnormalities were found in the brain of B2. Examination of the peripheral nerves, eyes, and inner ears of all 3 cats revealed no significant lesions. The skeletal muscles of the hind limbs of 1 cat (O1) contained large numbers of sarcocysts unassociated with an inflammatory response or necrosis.

Electron microscopic examination of the lateral cuneate nucleus of O1 confirmed that the spheroids seen with light microscopy represented dystrophic axons. The axons were markedly enlarged, and there was severe thinning and fragmentation of the myelin layer (Fig. 4). The distended axons varied in cytoplasmic content. Most contained 1 or several of the following: mitochondria, membrane-bound osmiophilic bodies, intermediate filaments arranged both in bundles of parallel arrays and in disorganized swirls, and nonmembrane-bound vacuoles of various sizes. No abnormal lysosomes, suggestive of a storage disease, were noted. In some axons, the entire axoplasm was replaced by one or more large vacuoles and could only be identified

Figure 1. Multiple axonal spheroids (arrows) in the lateral cuneate nucleus of a cat with neuroaxonal dystrophy. HE stain. Bar = 20 µm.

Figure 2. Marked loss of Purkinje cells in the cerebellar cortex of a cat with neuroaxonal dystrophy. HE stain. Bar = 20 µm. Inset: Spheroid in granular layer of cerebellum. HE stain.
as axons because of the thin surrounding myelin layer. The central PAS-positive core seen with light microscopy corresponded ultrastructurally with accumulations of electron-dense, flocculent, amorphous material that could not be identified (Fig. 5).

**Discussion**

Neuroaxonal dystrophy described in this group of cats has many similarities to the previous report of FHND, including slowly progressive hind limb ataxia, light microscopic changes in the brain stem nuclei, and electron microscopic findings of dystrophic myelination and terminal axonal swelling. There are, however, many differences. In contrast to the previous report in which neuronal loss was seen in the spiral ganglion of the inner ear and spheroid formation was seen in the organ of Corti, there was no histologic evidence of inner ear damage or electrodiagnostic indication of inner ear dysfunction in the cats in this report. There was involvement of the nuclei in the cerebellum and spinal cord in the cats in this report, but similar involvement was not noted in the previous report. Although some of the affected cats in this report had diluted coat color, abnormal coat color was not consistently associated with the syndrome. There was also a difference in the age of onset of clinical signs. Clinical
signs occurred by 5-6 weeks of age in the previous report but were not noted until 7-9 months of age in this report.

There are 2 possible reasons for the later onset of clinical signs: 1) because these cats were barn cats they may not have been as closely scrutinized as the cats from the previous study and as a result, clinical signs may not have been noticed until they were relatively severe and 2) this case may represent the later onset syndrome as is seen in neuroaxonal dystrophy in humans. In humans, hereditary neuroaxonal dystrophy occurs in 2 syndromes that differ mainly by age of onset of clinical signs. Infantile neuroaxonal dystrophy has an onset of clinical signs at about 6 months of age, whereas juvenile neuroaxonal dystrophy is usually first diagnosed at around 9 years of age. Both of these syndromes are characterized by a period of normal early development followed by a sudden onset of incoordination and ataxia. Visual, auditory, and mental deficits have also been described. Similarly, neuroaxonal dystrophy may manifest as various syndromes within domestic species. In dogs, various syndromes characterized by neuroaxonal dystrophy have been described. Neuroaxonal dystrophy has been described in Rottweiler dogs, Bull Mastiff dogs, and Collie Sheepdogs. In each of these breeds, the syndrome differs in age of onset of clinical signs and distribution of lesions. In all syndromes, however, autosomal recessive transmission is suspected. In Rottweiler dogs, the histologic changes are very similar to those seen in the cats in this report in that massive numbers of axonal spheroids are seen in brain stem nuclei and in the spinal cord, and the gracilis nucleus and the cuneate nucleus are severely involved. There is also involvement of the dorsal horn of the spinal cord, loss of Purkinje cells in the cerebellum, and spheroid formation in the granular layer of the cerebellar cortex. Clinical signs are first noticed within the first year of life, usually around 6 months of age. Neuroaxonal dystrophy in Collies is characterized by spheroid formation primarily in the cerebellum, with little involvement of the brain stem nuclei. Clinical signs develop earlier, usually between 2 and 4 months of age, than in Rottweilers. Neuroaxonal dystrophy confined to the cerebellum has also been described in Bull Mastiff puppies, and affected dogs usually first show clinical signs between 4 and 9 weeks of age. The syndrome is associated with severe hydrocephalus.

In horses, neuroaxonal dystrophy also manifests as 2 distinct syndromes. In equine degenerative myelonecephalopathy (EDM), clinical signs of disease first appear at around 3 years of age. Microscopically, axonal degeneration is found diffusely through the dorsolateral and ventromedial funiculi of the cranial cervical and midthoracic segments of the spinal cord. Spheroid formation is seen in the cuneate nucleus and the gracilis nucleus of the brain stem and in the thocolumbar nuclei in the gray matter of the spinal cord. The cause of EDM is unknown, but both heredity and vitamin E deficiency may contribute to this condition. Neuroaxonal dystrophy of the accessory cuneate nucleus in Morgan horses is characterized by...
neuroaxonal dystrophy, vacuolization, and gliosis localized in the accessory cuneate nucleus, with minimal or no changes in the spinal cord and remaining brain stem. The age at onset of clinical signs ranges from 6 months to 3 years. Frequently, affected horses are related.

Neuroaxonal dystrophy in Suffolk and Merino sheep is similar in age of clinical onset. The conditions differ, however, in lesion distribution. Spheroid formation is seen in the spinal cord in Merino sheep but not in Suffolk sheep. In both breeds, the disease is thought to be transmitted by an autosomal recessive gene.

The previous report of neuroaxonal dystrophy in cats involved a study of 6 litters and concluded that there was an autosomal recessive mode of inheritance. Although there is no proof of inheritance in the present case, the similarity to other hereditary neuroaxonal degenerative disorders and the fact that siblings from several litters born to the same queen were affected suggests an inherited disorder. Although serum α-tocopherol levels were not evaluated in this study, vitamin E deficiency should also be considered as a possible cause. Low serum α-tocopherol levels have been reported in cases of EDM. In rats, chronic vitamin E deficiency results in spheroid formation in the gracile and cuneate nuclei of the brain stem and in skeletal muscle degeneration. Skeletal muscle degeneration was not seen in the cats in the present study. In addition, the other barn cats in the colony that were being fed an identical commercial diet failed to develop this syndrome.

The pathogenesis of neuroaxonal dystrophy is still unclear. This condition can manifest in various different syndromes, even within the same species. The disease seen in the cats in this report may represent one of several manifestations of neuroaxonal dystrophy in cats: one that has a wider lesion distribution than the one previous report, is not always associated with abnormal diluted coat color, and has a later age of onset of clinical signs.

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References