Clinicopathologic and magnetic resonance imaging characteristics associated with polioencephalomyelopathy in a ShihTzu

Marc Kent, DVM, DACVIM; Simon R. Platt, DVM&S, DACVIM; Raquel R. Rech, DVM, PhD; Dharshan Neravanda, DVM; Elizabeth W. Uhl, DVM, DACVP, PhD; Scott J. Schatzberg, DVM, DACVIM, PhD

Case Description—A 17-month-old 7-kg (15.4-lb) Shih Tzu was evaluated because of progressive thoracic limb weakness of 3 months’ duration.

Clinical Findings—Neuroanatomic diagnosis was consistent with a lesion affecting the cervicothoracic (C6 through T2) spinal cord segments. Electrophysiologic testing revealed abnormal spontaneous activity in the thoracic limbs. Via magnetic resonance (MR) imaging, a lesion in the spinal cord that extended from the C5 through C7 vertebrae was detected, as were symmetric lesions in the cranial portion of the cervical spinal cord, caudal colliculi, and vestibular and cerebellar nuclei. Tests to detect metabolites indicative of inborn errors in metabolism revealed no abnormalities.

Treatment and Outcome—Prior to undergoing MR imaging, the dog received clindamycin (14 mg/kg [6.4 mg/lb], PO, q 12 h), trimethoprim-sulfadiazine (17 mg/kg [7.7 mg/lb], PO, q 12 h), and prednisone (1 mg/kg [0.45 mg/lb], PO, q 24 h). Because of its deteriorating condition, the dog was euthanized. During necropsy, gross lesions were identified in the cervical spinal cord, caudal colliculi, and vestibular and cerebellar nuclei (corresponding to lesions detected via MR imaging). Microscopic evaluation of the brain and spinal cord revealed polioencephalomyelopathy; there was severe spongiosis of the neuropil with reactive astrocytes (many with high numbers of swollen mitochondria) and preservation of large neurons.

Clinical Relevance—The form of polioencephalomyelopathy in the Shih Tzu of this report was similar to that described for Australian Cattle dogs; the similarity of findings in dogs with those in humans with Leigh disease is suggestive of a mitochondrial defect. (J Am Vet Med Assoc 2009;235:551–557)

A 17-month-old 7-kg (15.4-lb) Shih Tzu was evaluated at the University of Georgia because of a 3-month history of progressive thoracic limb weakness. On physical examination, no abnormalities were evident. Neurologic examination revealed apparently normal mentation. The gait in the thoracic limbs was short strided. When standing, the thoracic limbs would frequently splay out and the dog would collapse. No gait abnormalities were identified in the pelvic limbs. Postural reactions were delayed in the thoracic limbs but were considered normal in the pelvic limbs. There was marked muscle atrophy in the thoracic limbs, and muscle tone and withdrawal reflexes were decreased; however, muscle mass, muscle tone, and patellar and withdrawal reflexes in the pelvic limbs appeared normal. The cutaneous trunci reflex was also considered normal. Results of cranial nerve evaluation were considered normal, and no signs of pain were elicited during manipulation of the neck. Neuroanatomic findings were consistent with a lesion in the gray matter of the C6 through T2 spinal cord segments, ventral roots, spinal nerves, ventral branches, brachial plexus, or thoracic limb musculature because the lesion affected the thoracic limbs with no obvious involvement of the pelvic limbs. A bilateral brachial plexus neuropathy or a diffuse neuromuscular disorder, primarily affecting the thoracic limbs, was considered a less likely neuroanatomic diagnosis. Differential diagnoses included poliomyelitis, neoplasm (glioma, nerve sheath, or lymphoma), brachial plexus neuritis, and myositis.

A CBC revealed lymphocytosis (3.12 × 10³ cells/µL; reference range, 0.4 × 10³ cells/µL to 2.9 × 10³ cells/µL). Results of serum biochemical analyses (including assessment of creatine kinase activity) and urinalysis were within reference limits. Thoracic radiography revealed no abnormalities. The dog had no detectable serum antibodies against Ehrlichia canis, Borrelia burgdorferi, Rickettsia rickettsii, Toxoplasma gondii, and Neospora caninum; it was also negative for anti-acetylcholine receptor antibody.

The dog was anesthetized, and EMG of the musculature of the thoracic limbs revealed abnormal sponta-

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>FLAIR</td>
<td>Fluid attenuated inversion recovery</td>
</tr>
<tr>
<td>GFAP</td>
<td>Gial fibrilar acid protein</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>TE</td>
<td>Time to echo</td>
</tr>
<tr>
<td>TR</td>
<td>Time to repetition</td>
</tr>
</tbody>
</table>

From the Departments of Small Animal Medicine and Surgery (Kent, Platt, Neravanda, Schatzberg) and Pathology (Rech, Uhl), College of Veterinary Medicine, University of Georgia, Athens, GA 30602. Address correspondence to Dr. Kent.
neous activity, fibrillation potentials, and positive sharp waves; no abnormalities were identified in the musculature of the pelvic limbs. On the basis of the abnormal EMG findings for the thoracic limbs, biopsy specimens of the lateral head of the left triceps brachii and left biceps femoris muscles were obtained. Histologic examination of tissue sections revealed scattered angular and atrophic myofibers in the triceps brachii muscle; both type I and type II myofibers were affected. However, abnormalities were not observed in the biceps femoris muscle specimen. The histopathologic changes in the triceps brachii muscle were most consistent with neurogenic atrophy, although a specific cause was not identified.

Because of the possibility of poliomyelitis or brachial plexus neuritis, the dog was treated for approximately 1 month with clindamycin (14 mg/kg [6.4 mg/lb], PO, q 12 h), trimethoprim-sulfadiazine (17 mg/kg [7.7 mg/lb], PO, q 12 h), and prednisone (1 mg/kg [0.5 mg/lb], PO, q 24 h). After the month of treatment, no clinical improvement was evident, and reevaluation 2 weeks later revealed progression of disease. At this time (6 weeks after the initial evaluation), the dog was tetraparetic and could only walk a few steps before the thoracic limbs collapsed. Mild to moderate upper motor neuron paresis and general proprioceptive ataxia in the thoracic limbs was unlikely because of the upper motor neurons that innervate the muscles of the thoracic limbs. Involve-
diagnosis was a lesion affecting the gray and white matter of the C6 through T2 spinal cord segments. Involve-
mnet of the nerves that innervate the muscles of the thoracic limbs was unlikely because of the upper motor neuron paresis and general proprioceptive ataxia in the pelvic limbs.

The dog was anesthetized for MR imaging of the cervicothoracic vertebral column. A 3.0-T MR imaging unit was used to obtain T2-weighted, T2-weighted FLAIR, and T1-weighted FLAIR images. For sagittal T2-weighted images, TR was 2,500 milliseconds, TE was 112 milliseconds, and echo train length was 23 echoes; for axial T2-weighted images, those settings were 4,000 milliseconds, 105 milliseconds, and 20 echoes, respectively. For sagittal T1-weighted FLAIR images, TR was 2,610 milliseconds, TE was 8 milliseconds, echo train length was 8 echoes, and time of inversion was 700 milliseconds; for axial T1-weighted FLAIR images, TR was 2,629 milliseconds, TE was 9 milliseconds, echo train length was 10 echoes, and time of inversion was 700 milliseconds. For sagittal T2-weighted FLAIR images, TR was 9,502 milliseconds, TE was 120 milliseconds, echo train length was 1 echo, and time of inversion was 2,250 milliseconds. For all images, slice thickness was 3.0 mm (without a gap), and images were acquired sequentially. Matrix size for all sequences ranged from 416 × 320 to 256 × 224. The T1-weighted FLAIR images were obtained before and after IV administration of gadopentetate dimeglumine (0.1 mmol/kg [0.05 mmol/lb]); an extremity coil (knee coil for use in humans) was used to obtain images of the vertebral column in the sagittal, transverse, and dorsal planes.

Magnetic resonance imaging revealed a well-de-
marcated, ovoid (2.4 × 0.5 × 1.0-mm), intra-axial le-
sion of the spinal cord, which resulted in expansion of the spinal cord from the midbody level of the C5 vertebra to the midbody level of the C7 vertebra. Another much smaller well-demarcated, intra-axial lesion was detected in the portion of the spinal cord within the C1 vertebra (Figure 1). In comparison with the normal spinal cord parenchyma, the lesions were hyperintense on T2-weighted and T2-weighted FLAIR images and

![Figure 1](image_url)

**Figure 1**—Sagittal and axial T2-weighted MR images of the cervical portion of the spinal cord in a 17-month-old Shih Tzu that was evaluated because of progressive thoracic limb weakness of 3 months’ duration. A—Sagittal T2-weighted image. In the spinal cord in the region of the C5 through C7 vertebrae, there is a large intra-axial area that is hyperintense (arrowhead), compared with the unaffected spinal cord parenchyma. B—Axial T2-weighted image obtained at the level of the dens of the C2 vertebra. C—Axial T2-weighted image obtained at the level of the C5-C6 intervertebral disk. In panels B and C, a hyperintense area of the spinal cord is visible bilaterally (arrow).
hypointense on T1-weighted FLAIR images. In the axial plane, the lesions were associated predominantly with the ventral column of gray matter. At the level of C1 and C3 vertebrae, the lesions were exclusively associated with grey matter in the ventral horns of the spinal cord bilaterally. Caudal to the C3 vertebra, the discrete bilateral lesions fused to form a single lesion that was associated with the ventral and central portions of the gray matter and the adjacent white matter of the spinal cord. On the sagittal T2-weighted images, hyperintense lesions were observed in the caudal colliculi and rostral medulla oblongata.

On the basis of these observations, the brain was examined by use of the same MR sequences. Bilateral symmetric lesions were identified in the caudal colliculi (3 × 3 × 3 mm), in the area of the vestibular nucleus in the medulla (5 × 3 × 4 mm), and in the medulla of the cerebellum (in the area considered to be the interposital nuclei [2 × 2 × 2 mm]; Figure 2). Compared with the unaffected gray matter of the brain, the lesions appeared hyperintense on T2-weighted and T2-weighted FLAIR images and hypointense on the T1-weighted FLAIR images. Following IV administration of gadolinium megluminate, no enhancement was observed in images of the lesions in the brain or spinal cord. A sample of CSF was collected from the cerebellomedullary cistern, and results of cytologic evaluation and measurement of protein content were considered normal. Based on the symmetric lesions identified via MR imaging, the primary differential diagnoses included nutritional deficiencies or excesses, an inborn error of metabolism, or toxicity. Neoplasia and inflammation were considered to be far less likely. Screening for inborn errors of metabolism was performed by testing a urine sample for abnormally high concentrations of metabolites, but no such abnormalities were detected.

Approximately 2 weeks later, the owner reported that the dog was vocalizing intermittently, especially when it was picked up. Additionally, a behavior change was noted that included aggressive chewing and licking of the left thoracic limb (which the owners suspected was associated with discomfort). The dog was treated with gabapentin (10 mg/kg [4.5 mg/lb], PO, q 12 h) and prednisone (1 mg/kg, PO, q 24 h) for potential neuropathic pain. Over a 2-week period, the dog became progressively weaker, and it eventually was unable to bear weight on the thoracic limbs. Manipulation of the neck elicited signs of pain. The owners elected euthanasia of the dog.

Necropsy revealed that the gross abnormalities were limited to the nervous system. The C5 through C7 spinal cord segments were more swollen (1.0 × 0.7 cm in diameter and 3.5 cm in length) than expected for the cervicothoracic intumescence in a clinically normal dog. On the cut surface, the gray matter in the area of the enlargement was effaced by an accumulation of gelatinous material. There were multiple, discrete, bilaterally symmetric, discolored (gray), malacic areas (up to 0.5 cm in diameter) in the gray matter of the caudal colliculi in the mesencephalon, interposital nuclei of the cerebellum, and vestibular nuclei of the medulla oblongata.

The brain and spinal cord were fixed in neutral-buffered 10% formalin prior to sectioning. Representative samples of the cervicothoracic intumescence also were fixed in a conventional primary fixative of 2% (para)formaldehyde and 2% glutaraldehyde in 0.1M phosphate buffer (pH, 7.3) for electron microscopy. After several washes in 0.1M phosphate buffer (pH, 7.3), the tissue samples were immersed in 1% osmium tetroxide in 0.1M phosphate buffer (pH, 7.3). Microscopically, the lesions in the cervicothoracic intumescence were the most advanced. The neuropil was extremely rarified and was reduced to a loose meshwork of prominent blood vessels and moderate numbers of foamy macrophages (gitter cells). Chromatolysis was observed in a few neurons, but overall, the neurons were well preserved. Immunohistochemical staining for GFAP and vimentin revealed strong staining of reactive astrocytes at the center of the lesion in the cervicothoracic intumescence. There was also a greater number of reactive astrocytes at the periphery of the lesions. Multiple astrocytes were characterized by intracytoplasmic vacuolation.

Electron microscopy revealed ultrastructural changes of the most severely affected areas, including extensive destruction of the neuropil and degeneration of the neuronal perikarya. Spongiosis areas contained macrophages that were distended with vacuoles, lipid, degenerated myelin, and laminated inclusions. Surviving axons were demyelinated and swollen. Reactive astrocytes with increased numbers of mitochondria, some of which were

Figure 2—Axial T2-weighted MR images obtained at various levels of the brain in the dog in Figure 1. A—Image obtained at a level through thepons and caudal mesencephalon. Notice that there are bilateral hyperintense areas in the caudal colliculi (arrow). B—Image obtained at a level through the medulla oblongata. Areas of hyperintensity in the vestibular nuclei (large arrow) and cerebellar nuclei (small arrow) are visible bilaterally. C—Image obtained at a level through the medulla oblongata at a location caudal to theimage level in panel B. Areas of hyperintensity (arrow) in the region of the vestibular nuclei are also visible bilaterally in this view.
remarkably swollen, also were identified. This latter finding was suggestive of a mitochondrial defect.

Similar histologic lesions also were observed in sections of the brain. Well-demarcated, bilaterally symmetric areas of severe spongiosis were present in the caudal colliculi, interposital nuclei of the cerebellum, and caudal and lateral vestibular nuclei. The affected areas were rarified with multiple oval to round, clear vacuoles (10 to 40 µm in diameter) in the neuropil. Neurons in these areas were fairly well preserved and had only mild degeneration of neuronal perikarya that was characterized by loss of Nissl substance. However, a few clear intracytoplasmic vacuoles were occasionally observed in the neurons. Moderate numbers of round to oval astrocytes with abundant slightly eosinophilic cytoplasm and an eccentric nucleus (gemistocytic astrocytes) were present in the affected neuropil (Figures 3 and 4). Vessels in the affected areas were prominent and had plump endothelial cells. Similar but less severe lesions were observed in the ventral horn of the C2 spinal cord segment. On H&E-stained sections, the lesions extended into the white matter of the spinal cord and consisted of occa-
sional axonal spheroids and a few digestion chambers. Immunohistochecmical staining with antibodies against myelin basic protein confirmed that the white matter was relatively intact, whereas in the gray matter, the myelin sheaths were dilated and rarified. The remainder of the nervous system was apparently normal histologically.

**Discussion**

In humans and other animals, the primary differential diagnoses for bilateral symmetric lesions of the CNS are metabolic in nature. For example, bilateral symmetric lesions in the CNS may result from inborn errors of metabolism, nutritional deficiencies or excesses, and toxicoses; however, the etiology commonly is not identified. In dogs and cats, thiamine deficiency may cause symmetric lesions in the brainstem. The lesions associated with thiamine deficiency appear hyperintense on T2-weighted and T2-weighted FLAIR MR images (compared with the unaffected gray matter of the brain) and become enhanced following administration of gadopentetate dimeglumine to the patient.

In pigs, symmetric lesions involving the gray matter of the spinal cord may develop as a consequence of selenium toxicosis. Myelinolysis can develop in association with rapid correction of hyponatremia, resulting in symmetric lesions in the thalamus. The lesions associated with myelinolysis typically are hyperintense on T2-weighted images, compared with unaffected areas in the thalamus. In the dog of this report, nutritional deficiencies or excesses were thought unlikely causes of the CNS lesions because the dog was fed a commercial diet. Moreover, no physical examination findings or clinicopathologic data were suggestive of nutritional deficiencies or excesses. Similarly, rapid correction of hyponatremia was excluded from consideration on the basis of the results of serum biochemical analyses.

Several degenerative disorders in dogs that are associated with symmetric lesions of either the gray or white matter of the nervous system have been described. Leukodystrophies result from a defect in myelin synthesis or maintenance and are associated with dysmyelination of the CNS, peripheral nervous system, or both. Leukodystrophies are typified by symmetric, regional white matter lesions, which in severely affected animals may lead to axonal necrosis. Several leukodystrophies in dogs have been reported including spongy degeneration of the CNS in Labrador Retrievers.

In affected Labrador Retrievers, symmetric, hyperintense lesions are evident in T2-weighted MR images and those hyperintense areas correlate well with white matter lesions detected during gross and histologic examination. A chronic leukoencephalomyelopathy in Rottweilers has been described, in which bilateral demyelinating lesions develop in the cervical spinal cord, brainstem, cerebellar peduncles, and optic nerves. Recently, a leukoencephalomyelopathy in Leonbergers has been described; on MR images, the lesions are discernible in the dorsolateral funiculi of the C2 spinal cord segment and appear as symmetric, hyperintense areas on T2-weighted images. Histologically, the lesions in affected Leonbergers are suggestive of a primary demyelinating disease that affects various spinal cord and brainstem tracts as well as cerebellar white matter, cerebral peduncles, and optic tract and radiation. In the Shih Tzu of this report, it was difficult to discern exclusive involvement of spinal cord gray matter via MR imaging, but the presence of lesions that were confined to gray matter nuclei suggested a polioencephalomyelopathy. Consequently, an antemortem diagnosis of a leukoencephalopathy was considered unlikely.

Degenerative polioencephalopathies have been reported sporadically in the veterinary medical literature. In dogs, the most extensively described inherited gray matter disorder is a subacute necrotizing polioencephalopathy of Alaskan Huskies. The disease is characterized by symmetric lesions in the thalamus that extend caudally, and an autosomal recessive or mitochondrial pattern of inheritance is suspected. A similar polioencephalopathy in Yorkshire Terriers has been described; in those affected dogs, bilaterally symmetric lesions are present in the thalamus and medulla oblongata. Several rare polioencephalopathies in dogs for which the definitive pathogenesis is uncertain but a metabolic basis is suspected have also been reported.

A hereditary polioencephalomyelopathy has been identified in Australian Cattle Dogs, which has striking gross and histopathologic, imaging, and ultrastructural similarities with the disease in the Shih Tzu of this report. In affected Australian Cattle Dogs, similar bilaterally symmetric gray matter lesions develop in the cerebellum; caudal colliculi; lateral vestibular, lateral cuneate, and lateral reticular nuclei; and cervicothoracic and lumbosacral intumescences. Lesions detected via MR imaging correlate with histologic lesions; compared with adjacent unaffected parenchyma, the lesions appear hyperintense on T2-weighted images, hypointense on T1-weighted images, and target-like with alternating hyperintense and hypointense bands on proton density-weighted images. In the Shih Tzu of this report, identification of spinal cord lesions via MR imaging prompted similar MR imaging of the brain; the authors suggest that MR imaging of the brain should be standard diagnostic practice when bilaterally symmetric spinal cord lesions are identified via MR imaging. The lesions detected via MR imaging were corroborated by findings of both gross and histologic evaluations of the brain and spinal cord.

In both the Shih Tzu of this report and Australian Cattle Dogs with polioencephalomyelopathy, histologic evaluation of brain and spinal cord tissues revealed that the lesions predominated in the neuropil and were extremely rarefied, essentially composed of a loose meshwork of blood vessels, astrocytic processes, and demyelinated axons, with conspicuous lack of damage to the large neurons, even in the most severely affected regions. The sparing of large neurons is somewhat unique because symmetric diseases of the CNS typically are marked by prominent degenerative lesions of the neuropil, neurons, axons, and myelin. Similar to findings in affected Australian Cattle Dogs, the lesions in the Shih Tzu were characterized by extensive loss of neuropil with minimal neuronal loss, even within the cervicothoracic intumescence, which was the most severely affected area. Another histopathologic similarity between the dog of this report and Australian Cattle
Dogs with polioencephalomyelopathy was the presence of reactive astrocytosis, which was most prominent around the periphery of the lesions. However, 1 difference between the Shih Tzu and the affected Australian Cattle Dogs was a greater involvement of the white matter of the spinal cord in the former. Given the similar histopathologic changes in the dog of this report and Australian Cattle Dogs with polioencephalomyelopathy, investigation of the CNS lesions by use of electron microscopy was undertaken.

The ultrastructural changes observed in the CNS of the Shih Tzu also had marked similarities with those detected in Australian Cattle Dogs with polioencephalomyelopathy. In both breeds, the mitochondrial proliferation was present in astrocytes, which is most consistent with a mitochondrial defect. There are few reports of mitochondrial disorders in dogs, but those disorders typically result in myopathy that is characterized by the presence of ragged red fibers in muscles. Rarely, mitochondrial defects result in encephalopathy in dogs. Pathologic changes associated with a mitochondrial encephalopathy in dogs include abnormal mineralization of various areas of the brain. These are dementia, seizures, ataxia, and tremors. Similar to the suspected mitochondrial encephalopathies, T2-weighted MR imaging reveals bilaterally symmetric hyperintense areas in the thalamus, basal nuclei, dorsal portion of the brainstem, and cerebellar nuclei.

In a West Highland Terrier with L-2-hydroxyglutaric aciduria, similar lesions were evident via MR imaging. A Cavalier King Charles Spaniel with an organic aciduria involving excessive excretion of hexanoylglycine has been reported, but for that disorder, the lesions are not detectable in MR images.

In dogs and cats, a diagnosis of an inborn error of metabolism is supported by the presence of abnormal metabolites in samples of urine. Although the definitive diagnosis of mitochondrial disorders requires mitochondrial DNA and enzyme activity testing, results of the evaluation of urine organic acids may provide supportive evidence. The lack of detectable organic acid or amino acid abnormalities in urine of the dog of this report does not definitively exclude an inborn error of metabolism, but the negative finding argues against such a biochemical disorder as the underlying pathophysiologic process.

As evidenced by the dog of this report, detection of bilaterally symmetric spinal cord lesions via MR imaging should prompt similar examination of the brain. The lesions in this Shih Tzu and those associated with polioencephalomyelopathy in Australian Cattle Dogs were highly similar. Proton MR spectroscopy should be considered for evaluation of suspect cases of metabolic encephalopathy in dogs, based on pathologic similarities with Leigh disease in humans. Dogs with suspected inborn errors in metabolism also should be screened by use of biochemical testing to establish the possibility of an underlying mitochondrial defect. Postmortem assessments should include ultrastructural examination of the CNS tissues to determine whether affected dogs had mitochondrial abnormalities.

References