A Novel Leukoencephalomyelopathy of Leonberger Dogs

A. Oevermann, T. Bley, M. Konar, J. Lang, and M. Vandevelde

Many different degenerative diseases of the canine central nervous system (CNS) have been described involving white matter in various breeds.1–3 These include Afghan Hound myelopathy and a similar disease in Kooiker dogs, globoid cell leukodystrophy of various breeds, oligodendrogial dysplasia in Bullmastiffs, cavitating leukodystrophy of Dalmatians, hound ataxia, leukoencephalomyelopathy of Rottweiler dogs, and myelopathies in Jack Russell and Fox Terriers.4–15 In the Leonberger dog, no degenerative diseases of the nervous system have been described apart from an inherited polyneuropathy.16 This report describes the clinical signs, magnetic resonance imaging (MRI) findings, and neuropathology of a novel neurodegenerative disorder affecting the white matter of brain and spinal cord in 2 Leonberger dogs.

Case Histories, Clinical Examination, and MRI Findings

Case 1

A 2.5-year-old female Leonberger dog was referred to the small animal clinic of the Vetsuisse Faculty-Bern with a 1-year history of intermittent and spontaneous knuckling in the thoracic limbs. Three months before presentation, these signs began to worsen and include the thoracic limbs. The ataxia improved transiently after treatment with corticosteroids. On presentation, the bitch showed generalized ataxia and a hypermetric gait of the thoracic limbs with proprioceptive deficits in all limbs. On wheelbarrow examination, stiff stilted steps were obvious. The patellar reflex was increased on both sides and a crossed extensor-flexor reflex could be elicited from the pelvic limbs. Spinal reflexes were slightly diminished in the thoracic limbs. Hematology, serum biochemistry, and cerebrospinal fluid (CSF) analysis were within normal limits.

MRI of the head and C1–C4 was performed under general anesthesia in dorsal recumbency. Sequences included a sagittal (Time of Repetition [TR] Echo Time [TE] 2,850/125 ms) and transverse (TR/TE 5,958/100 ms) T2-weighted (T2W), a dorsal CSF-suppressing FLAIR-sequence (TR/TE/Time of Inversion 8,031/125/1,900 ms) and transverse (TR/TE 30/15 ms) and dorsal (TR/TE 30/12 ms) T1-weighted (T1W) gradient echoes—each before and after the IV administration of contrast agent (Omniscan®; 0.15 mmol/kg BW). Most obvious in transverse T2W images and less so in the FLAIR images was a hyperintense signal intensity within the dorsolateral funiculi of the spinal cord. The lesion was bilaterally symmetrical and extended from C1 to C4, becoming less intense caudally (Fig 1). Both the plain and contrast-enhanced T1W images were unremarkable.

Case 2

A male 2-year-old Leonberger dog was presented to the small animal clinic of the Vetsuisse Faculty-Bern with a history of generalized dysmetria of 6 months duration. The signs had worsened progressively over the past several weeks with spontaneous stumbling. Blood biochemistry and hematologic results examined 2 months before presented, these signs began to worsen and include the thoracic limbs. The ataxia improved transiently after treatment with corticosteroids. On presentation, the bitch showed generalized ataxia and a hypermetric gait of the thoracic limbs with proprioceptive deficits in all limbs. On wheelbarrow examination, stiff stilted steps were obvious. The patellar reflex was increased on both sides and a crossed extensor-flexor reflex could be elicited from the pelvic limbs. Spinal reflexes were slightly diminished in the thoracic limbs. Hematology, serum biochemistry, and cerebrospinal fluid (CSF) analysis were within normal limits.

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Fig 1. Dog 1. Transverse T2W (FSE T2, TR/TE 5,958/100 ms) image at the level of the atlantoaxial joint. Both lateral funiculi of the spinal cord show increased signal intensity (arrows).
previous were unremarkable except for serum T4 concentration (1.4 μg/dL; reference range 1.3–3.7 μg/dL) and serum TSH concentration (1.53 ng/mL; reference range 0–0.32 ng/mL) leading to the diagnosis of hypothyroidism. The dog was treated with levothyroxine (20 μg/kg body weight PO q12h) for 2 months. On neurologic examination, the dog had an abnormal gait with severe generalized ataxia, dragging its paws and with intermittent spontaneous knuckling and hypermetria of the thoracic limbs. Spinal reflexes were normal to increased in all limbs. CSF analysis was unremarkable.

MRI of the cervical spine (C2–C7) was performed under general anesthesia in dorsal recumbency. Sequences included a sagittal and transverse T2W and a dorsal T1W plain and contrast-enhanced gradient echo. Contrast application was the same and sequence parameters were similar as described for case 1. The only lesions were seen in the dorsolateral funiculi of the C2 segment, were symmetrical and hyperintense on T2, and did not contrast enhance.

In both dogs, a neurodegenerative disorder was suspected because of the symmetry of the lesions and the lack of contrast uptake. Leukodystrophy, neuroaxonal dystrophy, axonopathy, and leukoencephalomyelopathy were included in the list of differential diagnoses. Myelitis was considered less likely because of lack of both contrast uptake and signal changes in T1W images.

Both dogs were treated with physiotherapy (eg, controlled walking, passive extension and flexion of the limbs, massage), but had to be euthanized because of progressive deterioration of the disease 2 weeks and 5 months later, respectively.

**Neuropathology**

Complete necropsies were performed on both dogs shortly after euthanasia. Gross lesions were restricted to the spinal cord and brainstem. These consisted of an opaque and well demarcated, bilaterally symmetrical, whitish discoloration of the lateral columns (Fig 2). However, unilateral lesions or an asymmetrical pattern were observed as well at some levels (lateral corticospinal tract of the thoracic cord in dog 1, lateral corticospinal tract of the cervical and thoracic cord in dog 2). Lesions were most severe in the cervical spinal cord, but could be observed grossly also throughout the thoracic spinal cord and extending rostrally into the pyramidal tracts of the brainstem in both dogs. Brain, spinal cord, and representative tissue samples of internal organs were fixed in 10% neutral-buffered formalin, processed, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (HE). Selected sections of the brain and spinal cord were stained with luxol fast blue HE and modified Bielschowsky stain. Semithin sections from plastic-embedded tissues were stained with toluidine blue. Immunohistochemistry was performed with specific antisera against the 70 kDa subunit of human neurofilament (1:50, clone 2F11b) and glial fibrillary acidic protein (1:1,000, polyclonal anti-GFAP). The LSAB-AEC method was used, resulting in a red immunopositive reaction product at the site of the reaction.

Histologically, in both dogs the cervical spinal cord was most severely affected, but lesions extended caudally into the thoracic spinal cord and rostrally into the brain. Lesions were most prominent in the lateral corticospinal tract, but encroached on the dorsal spinocerebellar, rubrospinal, and the lateral spinothalamic tracts. In case 1, lesions were observed also at the periphery of the fasciculus cuneatus in the cervical spinal cord. A subpial rim of white matter was always preserved. In the brain, lesions were confined to specific regions. Most severely affected areas included the cerebrospinal tract, tectospinal tract, pyramidal decussation, pyramids, medial lemniscus, and the spinal tract of the trigeminal nerve at the level of medulla oblongata. Furthermore, lesions were observed in the cerebellar white substance, cerebral peduncles, optic radiation, and optic tract. Lesions were predominantly bilaterally symmetrical, although in some areas a marked asymmetry could be observed (spinal tract of the trigeminal nerve in dog 1, lateral corticospinal tract of the thoracic cord in dog 1, lateral corticospinal tract of the cervical and thoracic cord in dog 2, pyramidal decussation in dog 2). The lesions were not uniform in intensity within certain functional systems (eg, lateral corticospinal tract, spinal tract of the trigeminal nerve in dog 1).

The affected areas showed a marked loss of myelin, readily visible in HE-stained sections because of a paler eosinophilic staining of the affected white matter areas. With luxol fast blue-HE staining, the deep blue staining of the normal white matter was replaced by an eosinophilic staining (Fig 3). Myelin loss was replaced by a prominent gliosis with numerous GFAP-positive reactive fibrillary and gemistocytic astrocytes (Fig 4). Microscopically, dilated myelin sheaths often contained stellate cells, and a few scattered swollen axons were observed. However, axonal changes were relatively mild and confined to the areas of severe myelin loss. Furthermore, Bielschowsky stain and immunohistochemistry for neurofilaments revealed numerous preserved axons running through the

![Fig 2. Dog 1. Transverse section of the cervical spinal cord. Bilaterally symmetrical foci of whitish and opaque discoloration in the lateral funiculi.](image-url)
affected areas (Fig 5). In dog 2, lesions in the spinal tract of the trigeminal nerve and in the spinal cord were accompanied by a few mild lympho-histiocytic cuffs around the vessels. Minimal Wallerian degeneration was observed rostrally and caudally from the lesions in the spinal cord as well as in the central white matter of the brain. Semithin sections essentially confirmed the demyelinating nature of the lesions with myelin phagocytosis and naked axons. Numerous thin myelin sheets indicated remyelination (Fig 6). No lesions were observed in peripheral nerves.

Discussion

A novel demyelinating disorder in Leonberger dogs is described affecting both sexes. The neurologic deficits can be explained by demyelination caused by slowing or complete blocking of conduction along affected nerve fibers. Ataxia was most likely caused by involvement of the general proprioceptive system, including the medial lemniscus and the fasciculus cuneatus. Increased extensor tone, crossed extensor reflex, stiff limb protraction, and toe dragging could be explained by the involvement of the lateral corticospinal and rubrospinal tracts. The lesions in the optic system and central trigeminal tracts probably were not severe enough to cause related neurologic signs.

Myelin breakdown was the most prominent change, and axons were largely preserved, suggesting a primary
demyelination. The few swollen axons were interpreted to be secondary to severe myelin loss. Myelin degenerative disorders can be classified into either dysmyelination (leukodystrophy) or myelinolytic diseases. The former refers to inherited conditions in which myelin synthesis is defective and cannot be maintained. The latter is characterized by disintegration of initially normally formed myelin. Although the restricted distribution and the late onset of clinical signs would favor the latter, it remains to be established if the myelin loss in the 2 Leonberger dogs is caused by a dysmyelination (leukodystrophy) or a myelinolytic disorder. Therefore, the more general term leukoencephalomyelopathy was chosen to describe this degenerative disorder. The similarity of the history, clinical signs, and pathologic lesions in 2 dogs of the same breed suggests a genetic basis of the disorder, although pedigree analysis of the 2 Leonberger dogs revealed no common ancestors and none of the littermates seemed to be affected as far as we could determine.

The disorder described here shows striking clinicopathologic similarities to the leukoencephalomyelopathy described in Rottweilers. Clinical signs in Rottweilers include, as in the Leonberger dogs, progressive ataxia of all 4 limbs, proprioceptive deficits, and thoracic limb hypermetria. The age of onset in Rottweilers varied between 1.5 and 3.5 years. Furthermore, the type and distribution of lesions are almost identical with only mild variations. In Rottweilers, a genetic basis for the disorder has been suggested because of the familial relationship among the dogs, but the mode of inheritance could not be elucidated. The lesions in both breeds are clearly demyelinating. Simultaneous vigorous remyelination suggests that the oligodendrocyte/myelin compartment is not fundamentally destroyed. Rather, myelin sheets are produced but appear to be unstable. Puzzling for a primary demyelinating disease in the Rottweilers and Leonbergers is the restricted distribution of the lesions, seemingly confined to certain functional systems, reminiscent of multisystem degenerations. This suggests that the primary defect is located in neurons or axons, perhaps hampering the intimate interaction between neurons and oligodendrocytes, where neurons fail to provide proper signals for maintaining the myelin sheets.

The molecular basis of such axon-myelin relationships during development and after injury has been investigated in recent years. The leukoencephalomyelopathy in Rottweilers and Leonbergers would provide an interesting model to study such neuron-myelin interactions.

The slowly progressive leukoencephalomyelopathy described here differs from the rapidly progressing hereditary myelopathy in Afghan Hounds and Kooiker dogs, which is restricted to certain segments of the spinal cord and characterized by prominent malacia and microcavitation of the white matter affecting all funiculi. Preserved axons running through the destroyed white matter in Afghan Hound myelopathy indicate a primary myelin degeneration, whereas prominent Wallerian degeneration in the Kooiker dogs is more indicative of axonal disease. Hound ataxia, a progressive myelopathy described in Harrier Hounds, Beagle Hounds, and Foxhounds, and hereditary ataxia of Fox and Jack Russell Terriers all are characterized by primary axonal degeneration, which was not a feature in the Leonberger dogs described here.

In conclusion, this novel leukoencephalomyelopathy of Leonberger dogs appears to be a primary demyelinating disorder that has to be included in the differential diagnosis for ataxia in this breed. The inherited polyneuropathy occurring in this breed can be ruled out because of the lack of predominant lower motor neuron signs and abnormalities in the peripheral nerves. Compressive lesions and inflammation can be ruled out by imaging and CSF examination, respectively. MRI examination facilitates obtaining an in vivo diagnosis. No similar symmetric hyperintense MRI lesions of the spinal cord of dogs have been reported. In people, T2W hyperintense symmetric lesions of the cervical spinal cord have been associated with cobalamin deficiency (subacute combined degeneration), copper deficiency, Wallerian degeneration, amyotrophic lateral sclerosis, spinocerebellar atrophy, poliomyelitis (affecting mainly gray matter), AIDS myelitis, and multiple sclerosis. The signal intensity changes are caused by demyelination, Wallerian degeneration, and gliosis. Pathologic examination in the 2 cases revealed additional findings in the brain not detected on MRI.

At this time, it appears that the disease in Leonberger dogs could be an inherited myelinolytic disorder. Recognition of additional cases and their pedigree analysis in combination with test matings might help to establish the genetic base of the disease.

Footnotes

a Omniscan; GE Healthcare AS, Oslo, Norway
b DAKO, Glostrup, Denmark

References