

Congenital Tremor With Spongy Degeneration of the Central Nervous System in Two Puppies

Martine Cachin, DVM, and Marc Vandeveld, DVM

Two crossbred puppies exhibited a generalized tremor that was accentuated by excitement or voluntary movement. Hypermetria was also present. Neurohistologic examination showed a bilaterally symmetric spongy condition, predominantly of the gray matter in the brain and spinal cord. These two dogs were different, both in their clinical presentation and histologic appearance, from other reported cases of spongy degeneration. The clinicopathologic correlation between spongy degeneration and tremor is unclear. Spongy degeneration should be included in the differential diagnosis of tremor syndromes in puppies. (*Journal of Veterinary Internal Medicine* 1991; 5:87-90)

CONGENITAL spongy degeneration of the central nervous system (CNS) results from a number of different diseases affecting various species. All have the common histologic feature of a spongy appearance in nervous tissue.

Two such diseases are recognized in children: spongy degeneration of Van Bogaert-Bertrand Type (also called Canavan's disease), an inherited disorder of uncertain etiology,¹ and maple syrup urine disease (MSUD), a congenital disorder of amino acid metabolism.² Congenital spongy degeneration has been described as a hereditary metabolic disease in calves.³⁻⁶ Sporadic cases have also been reported in dogs⁷⁻⁹ and cats.¹⁰

In this article, we describe two additional cases of spongy degeneration of the CNS in dogs. However, in both the distribution of the lesions and the clinical presentation these cases differed markedly from previously reported cases.

Case Report

Three male crossbred puppies from a litter of 11 were presented at five weeks of age. The dam was a Malinois shepherd dog; the sire was unknown. Eight of the puppies were killed just after birth because the owner only wanted to keep three puppies. The litter was the first born to the dam. Generalized trembling was first noticed by the owner in two of the puppies (dogs 1 and

2) at age three weeks. Clinical signs did not progress. The third puppy (dog 3) was clinically normal. Food and water intakes were normal in all three dogs. They were not vaccinated.

On physical examination, all three pups were thin and had dull hair coats. On neurologic examination, dogs 1 and 2 were alert and lively. They had a severe, coarse tremor involving the limbs, trunk, and head. The tremor was accentuated during voluntary movement and excitement but resolved at rest and during sleep. Both puppies had a wide-based stance. The tremor was so strong that the dogs had difficulty maintaining balance and tended to move backwards or to the side while attempting to walk. Their gaits were stilted, and hypermetria was pronounced in all limbs. A fine oscillating tremor was also noticed in the eyes of the puppies. The oculocephalic reflexes were delayed. Postural reactions were slightly hypermetric. Spinal reflexes were normal. No signs of neurologic disease were found in dog 3. This dog was not studied further. Hematologic and blood chemical findings in dog 1 were normal. Although a specific diagnosis could not be made, congenital dysmyelination was suspected. Because of the possibility of spontaneous improvement in some cases of dysmyelination, euthanasia was not initially recommended. However, dog 1 was killed with an overdose of pentobarbital one month later due to lack of improvement, and dog 2 was killed after 2 months. Reexamination of both pups just before euthanasia showed the clinical signs to be identical to those seen initially.

Complete necropsy examinations were performed on both dogs. Material was fixed for histopathology in 4% formaldehyde. After fixation, representative blocks of brain and spinal cord were processed for paraffin embedding, cut at 4 μ m, and stained with hematoxylin and eosin (H&E), luxol fast blue-cresyl echt violet, and luxol fast blue-Holmes silver impregnation. Selected sections were immunostained for glial fibrillary acidic protein (GFAP) using the unlabeled peroxidase antiperoxidase method.¹¹

From the Institute of Animal Neurology, University of Berne, Switzerland.

Reprint requests: M. Vandeveld, DVM, Institute of Animal Neurology, University of Berne, P.O. Box 2735 CH-3001 Berne, Switzerland.

No gross abnormalities were found. Neurohistologic findings were similar in both pups. Lesions were more pronounced in the pup with the longer survival time. A bilaterally symmetric spongy state was noted throughout the neuraxis, with predominant involvement of the gray matter. All layers of the cerebral cortex, especially the neocortex, were affected (Fig. 1). The white matter was relatively spared, with only the U-fiber region exhibiting some vacuoles. The basal nuclei and nuclei of the brain stem (Fig. 2) and cerebellum were equally affected, again with marked sparing of the white matter, with the exception of the rostral commissure.

A spongy state was also present in the lumbar and cervical swellings of the spinal cord gray matter. Vacuolation was much less intense in the cerebellar cortex. However, although the central cerebellar white matter was relatively normal, that of the foliar was markedly vacuolated (Fig. 3). The extensive vacuoles seen in the neuropil varied in size and shape and were often adjacent to neurons, small blood vessels, and astrocytic nuclei. Nerve cell bodies themselves were morphologically normal. There was no sign of either tissue destruction or phagocytosis. The number of glial cells appeared to be increased. Numerous clusters of pale astrocyte nuclei were seen. Staining for GFAP showed a marked increase of often hypertrophic astrocytes in many areas of spongy degeneration (Fig. 4), although not all vacuolated areas contained hypertrophic astroglia. Special stains for myelin and axons revealed no abnormalities. The CNS of both puppies were essentially normally myelinated (Fig. 3). Myelin staining intensity was reduced in the foliar white matter of the cerebellum only, where marked spongy changes occurred. There was, however, no sign of active demyelination. The axons in this area were also normal (Fig. 5). No lesions were seen in the peripheral nervous system.

Discussion

The present study describes two crossbred puppies with spongy degeneration of the CNS. The principal clinical signs were generalized tremor and hypermetria.

The main neurohistologic finding was a bilaterally symmetric spongy state of the gray matter throughout the neuraxis. There was no myelin loss except in the cerebellar foliar white matter. These histologic lesions have some features in common with other reported cases of congenital spongy degeneration. There is a certain similarity with Canavan's disease in children in whom severe vacuolation is seen in both gray and white matter of the brain and spinal cord. However, in children the white matter clearly is predominantly affected. In all cases of CNS spongy degeneration previously described in calves, dogs, and cats, the white matter was either more severely^{4-6,10} or exclusively⁷⁻⁹ affected. In most cases, loss of myelin was also noted.^{1,4,5,7,8} The relative sparing of the white matter in our cases suggests that this is a distinct syndrome.

The pathogenesis of congenital spongy degeneration is still unclear. Ultrastructural and histochemical studies have suggested that spongy degeneration is due to a metabolic disturbance associated with abnormalities in the

astroglial mitochondria.¹ Spongy degeneration can be caused by a number of toxins such as triethyltin, hexachlorophene, isoniazid, or cuprizone.^{12,13} In all of these intoxications, the spongy change affects predominantly the white matter. In the above-mentioned cases in animals and humans, a genetic cause has been shown^{1,2} or suspected.^{3,4,6,7,10} We had no reason to suspect a toxic cause in these puppies. It seems more likely that the disease was of congenital, perhaps hereditary, origin. Unfortunately, the sire remains unknown, precluding breeding trials with the same parents.

The predominance of tremor in our dogs distinguishes this condition from most other reported cases of congenital spongy degeneration in animals. Tremor has been noticed^{5,6,7} but is not a major sign in these diseases. Richards and Kakulas⁸ described a Silky Terrier puppy with high-frequency myoclonic spasms associated with excitement or voluntary movement that subsided at rest. However, spasms were limited to the muscles of the vertebral column. In the Samoyed puppy reported by Mason et al.,⁹ tremor was the main clinical sign. However, as was not so with our cases, histologic changes in this dog were limited to the white matter.

Congenital tremor can also occur in several metabolic diseases of the nervous system, such as storage disorders, but is most often associated with dysmyelinogenesis. Dysmyelinogenesis has been described in many breeds^{14,15} and is associated with coarse generalized tremor that is accentuated on voluntary movement and resolves at rest. Hypermetria is a common sign.

A disease of suspected autoimmune origin associated with tremor occurs in young mature dogs of small, often white, breeds (Maltese Terrier, West Highland White Terrier). Generalized tremor that is exaggerated by excitement and voluntary movement but does not always resolve at rest is the main clinical sign. Histologic examination reveals a mild encephalomyelitis with perivascular lymphoid cuffs.¹⁶

Tremor, therefore, can be associated with very different neural lesions. The physiologic explanation of tremor remains obscure. Although the tremor of cerebellar disease is also accentuated by voluntary movement, it is not as severe and is limited primarily to the head.¹⁶

It has been suggested that nonmyelinated fibers may show spontaneous electrical activity (ectopic excitation) with the resulting discharges spreading to neighboring axons (ephaptic spread).¹⁴ It is possible that perineuronal vacuolation, like that seen in our puppies, may have a similar effect. Although clinicopathologic correlations remain obscure, the cases reported here showed that spongy degeneration of the gray matter can be an additional cause of congenital tremor. Distinguishing the actual cause is desirable because the prognosis for dysmyelinogenesis may be favorable in some cases, whereas the prognosis for spongiform degeneration is probably poor.

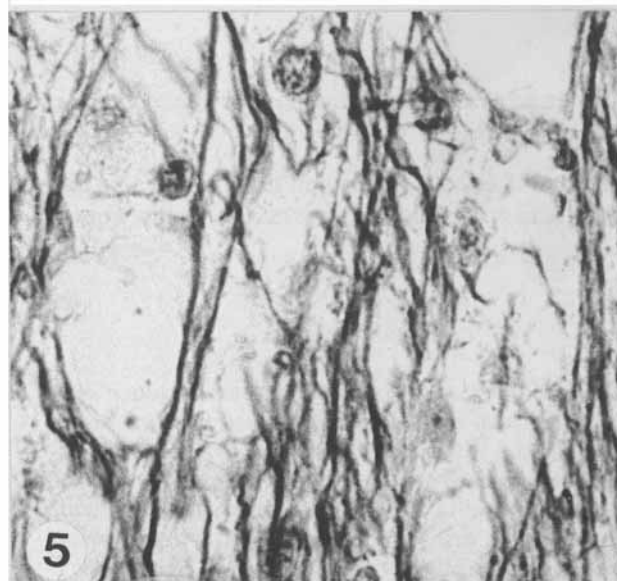
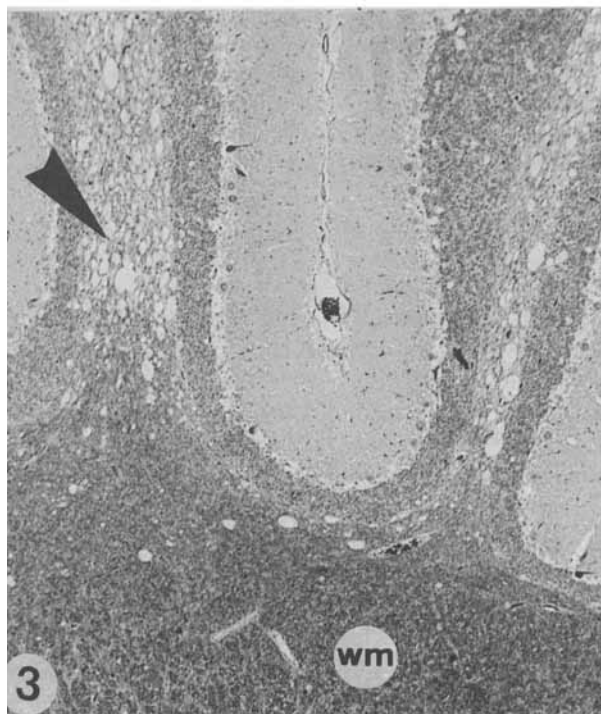
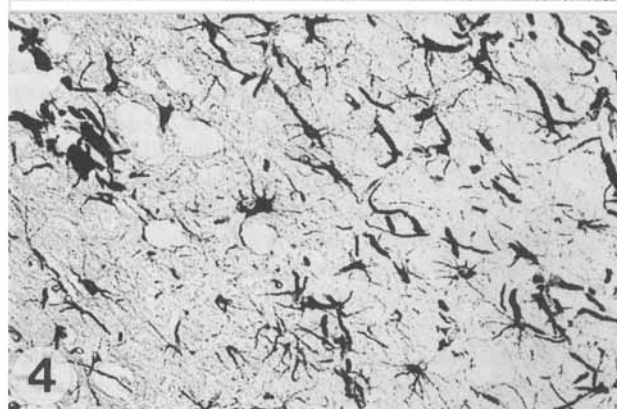
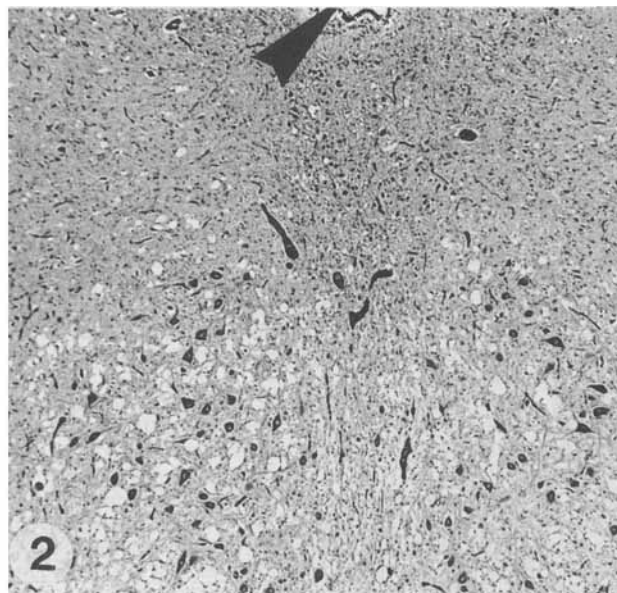


FIG. 1. Cerebral cortex with spongy state over the whole width. The subcortical white matter (WM) is not affected. (H&E, $\times 10$)

FIG. 2. Midbrain with bilaterally symmetrical spongy degeneration of the oculomotor nuclei. Mesencephalic aqueduct depicted by arrowhead. (H&E, $\times 40$)

FIG. 3. Cerebellum with spongy degeneration of the foliar white matter (arrow). Reduction of myelin staining intensity. The central white matter (WM) is normally myelinated. (Luxol fast blue-cresyl-echt violet, $\times 10$)

FIG. 4. Cerebral cortex with astrocytic hypertrophy. (Antigliab fibrillary acidic protein-PAP, $\times 100$)

FIG. 5. Cerebellar foliar white matter with spongy state showing separation of fibers. No degenerative changes of the axons. (Luxol fast blue-Holmes silver impregnation, $\times 750$)

Advanced techniques, such as magnetic resonance imaging and spinal evoked potentials, could be useful for definitive diagnosis.

References

1. Adachi M, Schneck L, Cara J, et al. Spongy degeneration of the central nervous system (Van Bogaert and Bertrand Type; Canavan's disease). *Hum Pathol* 1973; 4:331-347.
2. Rosenberg RN. Maple syrup urine disease. In: Rosenberg RN (ed.) *The Clinical Neurosciences*. New York: Churchill Livingstone, 1983; 132-133.
3. Cordy DR, Richards WPC, Stormont C. Hereditary neuraxial edema in Hereford calves. *Path Vet* 1969; 6:487-501.
4. Jolly RD. Congenital brain oedema of Hereford calves. *J Pathol* 1974; 114:199-204.
5. Duffel SJ. Neuraxial oedema of Hereford calves with and without hypomyelinogenesis. *Vet Rec* 1986; 118:95-98.
6. Harper PAW, Healy PJ, Dennis JA. Maple syrup urine disease as a cause of spongiform encephalopathy in calves. *Vet Rec* 1986; 119:62-65.
7. Zachary JF, O'Brien DP. Spongy degeneration of the central nervous system in two canine littermates. *Vet Pathol* 1985; 22:561-571.
8. Richards RB, Kakulas BA. Spongiform leucoencephalopathy associated with congenital myoclonia syndrome in the dog. *J Comp Pathol* 1978; 88:317-320.
9. Mason RW, Hartley WJ, Randall M. Spongiform degeneration of the white matter in a samoyed pup. *Aust Vet Pract* 1979; 9:11-13.
10. Kelly DF, Gaskell CJ. Spongy degeneration of the central nervous system in kittens. *Acta Neuropathol (Berl)* 1976; 35:151-158.
11. Sternberger LA. *Immunocytochemistry*, 2nd ed. New York: Wiley and Sons, 1979; 104.
12. O'Brien D. Spongy encephalopathies. *Proc 7th ACVIM forum*. 1989; 961-964.
13. Hall GA, Reid IM. The effects of hexachlorophene on the nervous system of sheep. *J Pathol* 1974; 114:241-246.
14. Duncan ID. Abnormalities of myelination of the central nervous system associated with congenital tremor. *J Vet Intern Med* 1987; 1:10-23.
15. Kornegay JN. Congenital and degenerative diseases of the central nervous system. In: Kornegay JN, ed. *Neurologic Disorders*. New York: Churchill Livingstone 1986; 124-125.
16. de Lahunta A. *Veterinary neuroanatomy and clinical neurology*, 2nd ed. Philadelphia: WB Saunders, 1983; 150.