SPONGIFORM DEGENERATION OF THE WHITE MATTER IN THE CENTRAL NERVOUS SYSTEM OF AUSTRALIAN CATTLE DOG LITTERMATES

Spongiforme degeneratie van de witte stof in het centraal zenuwstelsel bij Australische Herder pups

H. De Bosschere [1], M. Bos [1], R. Ducatelle [1], S. Bhatti [2], L. Van Ham [2]

[1] Department of Pathology, Bacteriology & Avian Diseases,
[2] Department of Small Animal Medicine
Faculty of Veterinary Medicine, Ghent University,
Salisburylaan 133, B-9820 Merelbeke, Belgium
Hendrik.debosschere@rug.ac.be

ABSTRACT

A spongiform degeneration of the white matter in 2 out of 8 Australian cattle dog littermates is described histologically. On the neurological examination, these dogs showed sternal decubitus, inability to walk and loss of coordination. A cerebellar ataxia was suspected. Microscopically, marked vacuolation of the white matter was observed in the cerebrum, cerebellum and dorsal funiculus of the spinal cord. A severe hypertrophy of astrocytes with pale and swollen nuclei and eosinophilic cytoplasm was also observed. This pathology has been described in several animals species but this is the first description in the Australian Cattle Dog.

SAMENVATTING

Een spongiforme degeneratie van de witte stof bij 2 van 8 Australische Herdershond pups wordt histologisch beschreven. Bij neurologisch onderzoek vertoonden deze pups sternale decubitus, onmogelijkheid om te stappen en verlies van coördinatie. Een cerebellaire ataxie werd vermoed. Microscopisch werd een uitgesproken vacuolisatie van de witte stof waargenomen het cerebrum, cerebellum en de dorsale funiculus van het ruggenmerg. Een erge hypertrofie van de astrocyten met een bleke, gezwollen kern en eosinofiel cytoplasma waren aanwezig.

Dit is de eerste beschrijving van deze aandoening bij de Australische Herdershond.

INTRODUCTION

Spongiform degeneration is a non-specific lesion in the central nervous system characterized by vacuolar disruption of the neuraxis without primary loss of neural elements (Jellinger and Seitelberger 1970). An inherited, progressive spongiform degeneration of myelin in the central nervous system in children is described as spongy degeneration of the van Bogaert-Bertrand type or Canavan's disease (Summers *et al.*, 1995).

Three patterns have been described in children: a congenital, an infantile and a juvenile form. At autopsy of these infants, the white matter is usually grayish and gelatinous. Microscopically, only the white matter is affected, showing a diffusely vacuolated aspect and staining pale with myelin stains. Structural abnormalities of the mitochondria within astrocytes have been suggested. Astrocytes regulate fluid and ion transport within the neuroparenchyma. Biochemical research on children with spongy degeneration revealed depressed levels of tissue aspartoacylase activity, which may be the underlying defect (Matalon *et al.*, 1988, Gascon *et al.*, 1990). In humans this condition is often viewed as a leukodystrophy, whereas in animals comparable syndromes have not so been categorized (Summers *et al.*, 1995).

Similar forms of spongiform degeneration of white matter have been described in several animal species, including Hereford calves (Jolly, 1974), Silkie terrier pups (Richards and Kakulas, 1978), Egyptian Mau

kittens (Kelly and Gaskell, 1978), Labrador Retriever pups (O'Brien and Zachary, 1985, Neer and Kornegay, 1995), a Samoyed pup (Mason and others, 1979) and Silver Foxes (Hagen and Bjerkås, 1990).

This is to our knowledge the first report of spongiform degeneration in the white matter of the Australian Cattle Dog breed to include the clinical and morphological observations.

CASE HISTORY AND CLINICAL EXAMINATION

Eight three-months-old Australian Cattle Dog littermates were presented with a two week history of progressive incoordination. There were five male and 3 female puppies in the litter. The males were said to be affected before the females were affected. The degree of incoordination varied from slight to obvious, with occasional head tremors. Some dogs were unable to walk and were presented in sternal recumbence. A complete physical and neurological examination was performed on the four most affected puppies.

Physical examination was normal except for slight (39.3°C, 39.3°C, 39.5°C) to obvious (40.2°C) elevation in body temperature. The results of the neurological examination were similar for all four puppies and can be summarized as follows: slow to absent postural reactions (conscious proprioception, hopping, visual and tactile placing reactions) in both fore and hindlimbs, with the forelimbs affected more than the hindlimbs. The menace reflex was absent in all dogs. The rest of the neurological examination was completely normal. A cerebellar ataxia was suspected.

In one puppy, anesthesia was induced with propofol and maintained with halothane in oxygen. A blood sample was collected from the jugular vein and a cerebrospinal fluid (CSF) sample from the cerebellomedullary cistern. Hematology and serum biochemistry were normal. There were no cells in the CSF (normal is less than eight per ml) and 17.5 mg % protein (less than 27.5).

As the prognosis of the puppies was poor, euthanasia of two puppies was suggested to perform a postmortem examination.

AUTOPSY AND HISTOLOGY

Immediately after death, tissue samples of the cerebrum, cerebellum, brainstem, spinal cord from the cervical, thoracal and lumbar regions, N. brachialis, N. femoralis and muscular tissue of a forelimb and a pelvic limb were collected for histological examination. Five micrometer sections of the 4 % formaldehyde-fixed and paraffin-embedded tissues were stained with hematoxylin and eosin (HE). An additional Luxol Fast Blue-Periodic Acid Shiff-Toluidin blue (LFB-PAS-Tol) staining for myelin was made of the neural tissue. Neural tissue of a normal dog of similar age was included as control tissue.

Macroscopically, both dogs had normal brain size and shape with sulci and gyri. Microscopically in both animals, the white matter of the cerebrum showed multiple areas of vacuolation and pale and swollen nuclei of the astrocytes with eosinophilic cytoplasm. In the cerebellum, a severe hypomyelination (LFB-PAS-Tol stain) and vacuolation of the white matter was observed, especially in the folia cerebri of the arbor vitae (Fig. 1), as compared to a control sample (Fig. 2). Especially the area adhering to the molecular layer of the cerebellum was affected. Astrocytes in the cerebellum had alterations similar to those in the cerebrum. The cervical, thoracic and lumbar spinal cord samples showed severe bilateral vacuolation of the white matter in the dorsal funiculus (radix dorsalis – dorsal sensory horn) (Fig. 3). In all affected areas, the vacuoles were round to ovoid in form and varied in size. In some regions it was assumed that larger cavities had been formed by coalescence of vacuoles. The majority of the vacuoles appeared empty, but sometimes scattered axons could be found. There was no significant vascular reaction or inflammation. All LFB-PAS-Tol stains of the central nervous system showed weak staining in the affected areas (Fig. 4) compared with the central nervous system of a normal dog of similar age (Fig. 5), while the spinal nerves and peripheral nerves (N. brachialis and N. femoralis) did not show hypomyelination or vacuolation. No histological abnormalities were observed in the peripheral nerves and muscular tissue of the limbs.

DISCUSSION

The clinical presentation of spongiform degeneration of the white matter varies between the different animal species. Inability to stand, and lateral and sternal recumbency were observed in Hereford calves (Jolly, 1974). A congenital tremor syndrome was described in Silkie terrier pups (Richards and Kakulas, 1978). Egyptian Mau kittens had pelvic limb ataxia with hypermetria (Kelly and Gaskell, 1978). Episodes of extensor rigidity of limbs, opisthotonic posturing and cerebellar ataxia were noted in Labrador Retriever pups (O'Brien and Zachary, 1985, Neer and

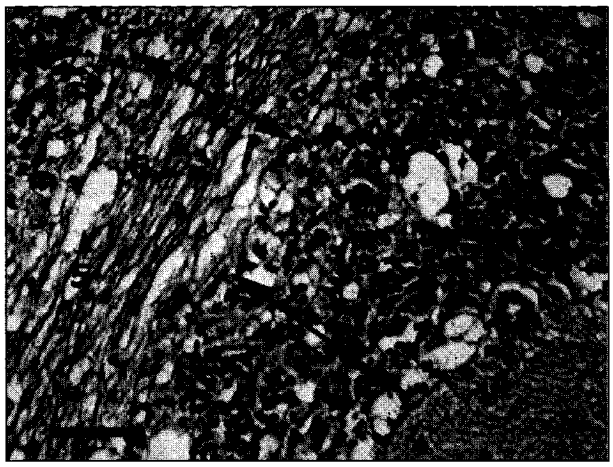

Fig. 1. Cerebellum of an affected dog. 1: hypomyelination of white matter / 2: granular layer / 3: molecular layer / 4: Purkinje cell / 5: spongiosis / 6: swollen astrocyte. HE staining. Bar = 250 µm.

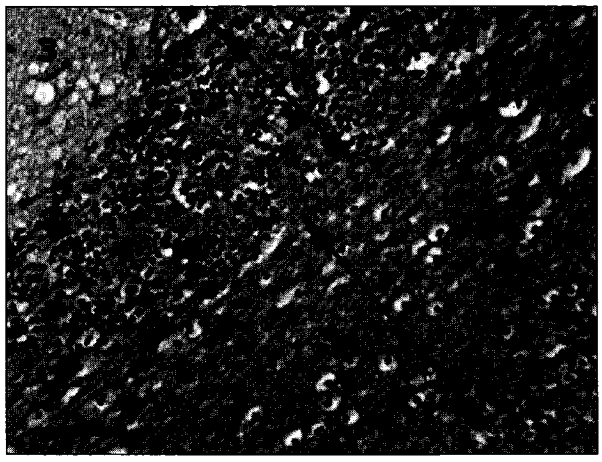

Fig. 2. Microphotograph of cerebellum of a control dog. 1: white matter / 2: granular layer / 3: molecular layer / 4: normal astrocyte. HE staining. Bar = 250 µm.

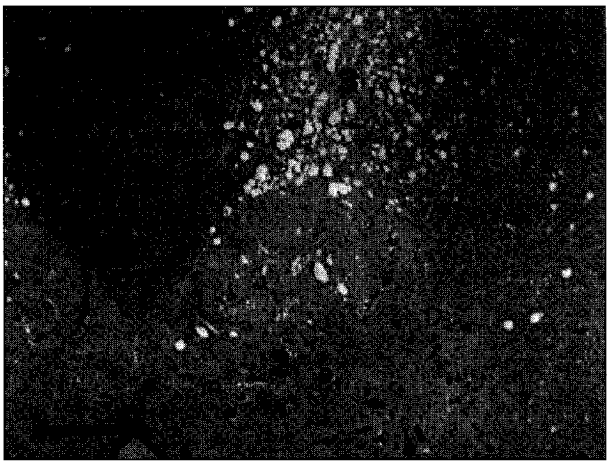

Fig. 3. Spinal cord section. 1: white matter/ 2: grey matter, dorsal horn / 3: hypomyelination of dorsal funiculus. HE staining. Bar = 1000 µm.

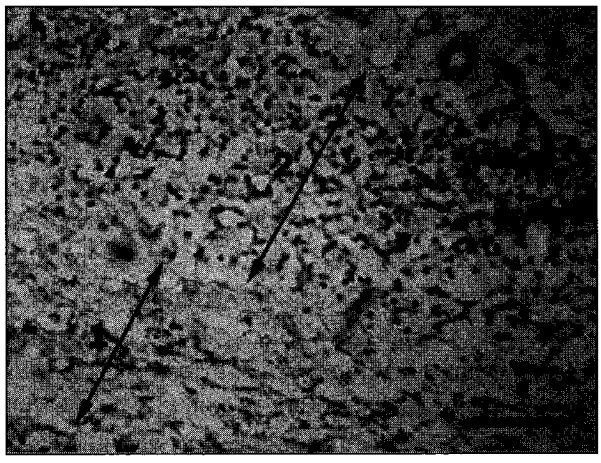

Fig. 4. Cerebellum of an affected dog. 1: hypomyelination of white matter / 2: granular layer / 3: molecular layer. LFB-PAS-TOL staining. Bar = 250µm.

Fig. 5. Cerebellum of a control dog.
1: white matter
2: granular layer.
LFB-PAS-TOL
staining. Bar = 250µm.

Kornegay, 1995). Generalized tremors were found in a Samoyed pup (Mason *et al.*,1979) and pelvic limb paresis and ataxia was seen in Silver Foxes (Hagen and Bjerkås, 1990).

The cerebellar and spinal ataxia of the littermates in the present case was due to spongiform changes of the white matter. In the present cases, hypomyelination and not demyelination was assumed since no indications of myelin degradation were found in the affected areas.

The microscopic lesions of spongy degeneration of the central nervous system reported in the literature vary, particularly as to the involvement of the gray matter in the spongy change. No gray matter was involved in the present case.

The present case resembles the congenital form of Canavan's disease in humans, since only white matter was affected and the onset of the nervous symptoms was at an early age. The congenital form has an autosomal recessive mode of inheritance in humans. However, the possible involvement of an infectious agent (canine distemper virus) cannot be totally excluded, although no clinical or histomorphological indications of a canine distemper virus infection were present. Typical observations of canine distemper encephalitis include the presence of intranuclear and intracytoplasmatic viral inclusion bodies within astrocytes, extensive lymphocytic inflammation of the white matter and elevated levels of protein and mononuclear cells in the cerebrospinal fluid (Summers *et al.*, 1995).

In the present case only the myelin of the central nervous system (white matter) was affected, while the spinal nerves and peripheral nerves did not show hypomyelinogenesis. The affected areas (white matter) may reflect a biochemical lesion that mainly affects fibrous astrocytes, while cortical (protoplasmic) astrocytes in the grey matter remain normal (Zachary and O'Brien, 1985). It is possible that an aspartoacylase deficiency as detected in children is the underlying defect in these Australian Cattle Dog litter mates, as well, but this was not investigated.

In conclusion, this is the second apparently hereditary central nervous system pathology to be described in the Australian Cattle Dog, following hereditary polioencephalomyelopathy (Brenner *et al.*, 1997), which primarily affects the gray matter.

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