A Progressive Spinal Myelinopathy in Beef Cattle

R. B. Richards and J. R. Edwards

Regional Veterinary Laboratory Department of Agriculture, Albany, Western Australia, 6330

Abstract. Ataxia of the hind limbs in nine calves was associated with degenerative lesions in spinal white matter and neuronal chromatolysis in red nucleus, spinal grey matter and various nuclei of the medulla oblongata and cerebellum. The clinical signs and lesions were similar to those observed in enzootic ataxia of red deer and occurred predominantly in calves of the Murray Grey breed. The pathogenesis appears to involve a primary defect in central nervous system myelin with progressive myelin loss primarily in the spinal cord.

There are few primary, non-inflammatory, myelinolytic diseases of the spinal cord recognized in domestic animals. An inherited progressive myelopathy occurs in Afghan hounds and a diffuse degeneration of spinal cord myelin has been described in two cats.

In ruminants, spontaneous spinal cord degeneration associated with ataxia has been described in goats, red deer, llama, wildebeeste and camel, and is well known in association with copper deficiency in sheep. There are few reports of degenerative spinal cord conditions in cattle. A syndrome of neonatal ataxia in calves associated with hypocupremia in cows was described in the USA, but no mention was made of spinal lesions. This paper describes a primary myelinolytic disease which differs from any previously reported condition in cattle.

Clinical History

Nine animals were derived from seven herds in the south coastal area of Western Australia which experiences a Mediterranean type climate. They were presented for routine diagnostic examination from 1975 to 1981. Seven of the calves were affected at birth and were females (Table 1). Most of the animals were of the Murray Grey breed which is derived mainly from the Angus and Shorthorn breeds.

The clinical appearance of all animals, with the exception of case 1 which was unable to stand at birth and was necropsied at one day of age, was remarkably similar. Most showed spinal ataxia manifested as incoordination of the pelvic limbs and a lateral swaying of the hind quarters when standing. A consistent observation was collapse of one hind limb with a tendency to fall to one side. Severely affected animals fell frequently and rose only with difficulty or required assistance to do so. Those with less pronounced clinical signs were able to suckle and graze successfully but usually adopted a wide-based stance of the pelvic limbs to maintain balance. These animals usually had an exaggerated action of the pelvic limbs when walking which was exacerbated when they were given forced exercise or otherwise excited. There was increased muscular tone in the pelvic limbs, but thoracic limb and cranial nerve functions were intact, and there were no signs suggestive of cerebellar dysfunction.

The clinical signs were progressive in all cases except for case 1. Case 9 had first shown failure to thrive and dragging of the hind limb toes at 12 months of age followed by staggering hind limb action, frequent falling and swaying of the hind quarters which became more intense over the following 12 months. Other animals had much more rapid progression of clinical signs. Case 3 was born with hind quarter weakness and incoordination and at 19 days of age was unable to stand even with assistance and seemed to have lost all control of the hind limbs.

Materials and Methods

The calves were killed by barbiturate overdosage, and the brain, spinal cord and a selection of major visceral organs from each were fixed by immersion in 10% neutral formalin. Brains were sliced at 5 mm intervals in the transverse plane and blocks from several areas selected for processing. Transverse and longitudinal blocks were taken from each spinal segment. Selected tissues were dehydrated, embedded in paraffin and sections cut at 6 μm. All sections were stained with hematoxylin and eosin (HE) and selected sections with luxol fast blue/periodic acid-Schiff (LFB/PAS), luxol fast blue/cresyl violet (LFB/CV), and luxol fast blue/silver (LFB/Ag). Frozen, formalin-fixed sections of spinal cord from cases 4, 5, 6 and 9 were also stained with Sudan black B, oil red O, phosphotungstic acid hematoxylin for nervous tissue, and Loyez stains.

Spinal cord and brain sections from a 10-week-old castrated male Murray Grey calf were similarly prepared for light microscopy to provide control specimens.

Copper estimations were conducted on liver samples from four calves and on the spinal cord from one by atomic absorption spectrometry after digestion in a mixture of nitric and perchloric acid. The results are expressed in ppm dry weight.

Results

A number of minor gross lesions were observed in several calves at necropsy (Table 2). Most were un-
related to the central nervous system, and all were regarded as incidental findings. However, an osseous malformation of the occipital bone in case 7 caused a mild compression deformity of the left lateral lobes of the cerebellum. This calf did not exhibit head tremor, thoracic limb placement abnormalities or any other sign of functional cerebellar deficiency when presented for examination at 4 months of age. There was mild dilatation of the third and lateral ventricles of the cerebrum in case 3, but this observation was considered insignificant compared to the microscopic lesions present in the spinal cord. There were no gross lesions in the brain or spinal cord of the other seven calves.

Microscopic lesions occurred in the spinal white matter of all calves, but only the lateral and ventral funiculi were consistently affected (Table 3). The lesions were bilaterally symmetrical, present throughout the length of the spinal cord, and generally affected all segments to the same degree. However, in two calves the lesions were more severe in the thoracic and lumbar segments than in other areas.

In all calves there was a distinct deficit of stainable myelin visible as ill-defined areas of pallor in hematoxylin and eosin-stained sections and more clearly demonstrated in luxol fast blue (Fig. 1) and Loyez preparations. The lesions were most severe in the lateral funiculi beneath the dorsal spinal nerve rootlet and in the ventral funiculi adjacent to the ventral median fissure. Peripheral white matter tracts were usually severely and diffusely affected, and there was relative sparing of those areas immediately adjacent to the spinal grey matter. The dorsal funicular lesions present in four calves affected both fasciculus gracilis and fasciculus cuneatus. The spinal lesions in young calves (cases 1–7) were characterized by numerous dilated myelin sheaths most of which contained axons of normal diameter (Fig. 2). Swollen axons were present in a small proportion of these fibers and some sheaths contained mononuclear macrophages. In longitudinal sections stained with LFB/Ag, axons were frequently seen traversing dilated segments of myelin tubes. Only occasionally were there segregated “digestion chambers” containing macrophages and cell debris typical of Wallerian degeneration (Fig. 3). In macrophages associated with Wallerian change, there was minimal positive staining for lipid material within spinal fibers in young calves. The density of glial nuclei in spinal lesions of the young calves was slightly increased.

Although the extent of the spinal lesions in older animals (cases 8 and 9) varied from mild to severe (Table 3), they were more advanced than in younger animals. There was less stainable myelin present in affected areas, and the ballooning dilation of surviving myelin sheaths was more pronounced (Fig. 4). Numerous dilated spaces in some areas gave the tissue a polycystic appearance. The distribution of lesions was similar to that seen in younger calves; the lateral and

---

**Table 2.** Summary of gross lesions seen at necropsy.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hemocysts on cardiac valves</td>
</tr>
<tr>
<td>2</td>
<td>Mild internal hydrocephalus</td>
</tr>
<tr>
<td>3</td>
<td>Patent ductus arteriosus</td>
</tr>
<tr>
<td>4</td>
<td>Small pulmonary abscess</td>
</tr>
<tr>
<td>5</td>
<td>Occipital bone deformity with compression of the cerebellum</td>
</tr>
<tr>
<td>6</td>
<td>Cutaneous dermatophilosis, mild focal interstitial nephritis</td>
</tr>
<tr>
<td>7</td>
<td>Cutaneous and esophageal papillomata, mild arthritis of left stifle joint</td>
</tr>
</tbody>
</table>

---

**Table 3.** Distribution and severity of histologic lesions in brain and spinal cord.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>White Matter Lesions in Spinal Cord*</th>
<th>Chromatolytic Neurons in Brain†</th>
<th>Cerebellar Roof Nuclei</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dorsal Funiculi</td>
<td>Lateral and Ventral Funiculi</td>
<td>Red Nucleus</td>
</tr>
<tr>
<td>1</td>
<td>--</td>
<td>++</td>
<td>n.s.</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>6</td>
<td>++</td>
<td>++</td>
<td>n.s.</td>
</tr>
<tr>
<td>7</td>
<td>+</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>n.s.</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>+</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

n.s. = not sectioned; -- = no lesion present.  
* = a small proportion of fibers (mainly peripheral) affected; ++ = a moderate proportion of fibers affected; +++ = a large proportion of fibers affected.  
† = -- affecting one or two neurons in each nucleus; ++ = affecting several neurons in each nucleus.
ventral funiculi had severe lesions, particularly in the peripheral regions. Most dilated spaces in the advanced lesions contained axons and were lined by a very thin layer of myelin. Non-myelinated (naked) axons were scattered throughout the lesions but were most numerous in the subpial region of peripheral white matter where there was substantial gliosis and thickening of the glia limitans (Fig. 5). The lateral spinal funiculi in case 9 contained a small quantity of stainable lipid in cells situated between surviving fibers, possibly in astrocytes. Spinal nerve rootlets in these sections showed normal myelination.

A few chromatolytic neurons were present in all spinal segments in all cases. They were usually present in the ventral grey matter horn but also occasionally in the dorsal nucleus of Clarke. There was no overt loss of neurons from the spinal grey matter.

Brain lesions were present in the medulla oblongata of most calves (Table 3) and consisted of white matter degeneration in spinocerebellar tracts, tectospinal tracts, and the median longitudinal fasciculus. These changes were similar to the lesions in spinal white matter. Chromatolytic neurons were often present in the red nucleus of the midbrain, the lateral vestibular nucleus, the medial portion of the reticular formation, and occasionally in the cerebellar roof nuclei. The chromatolysis was usually diffuse and involved some swelling of the cell body (Fig. 6), but convincing cell necrosis was not seen. The neuronal population of affected nuclei was subjectively assessed as normal. Dilated myelin sheaths, usually containing intact axons but sometimes containing macrophages, were seen in the cerebellar folial white matter in two calves. Changes in other tissues were consistent with the gross observations and considered to be incidental.

The liver copper concentrations were 295 ppm, 80 ppm, 5 ppm and 5 ppm in calves 3, 6, 9 and 8 respectively. Spinal cord copper in calf 3 was 2.82 ppm.

Discussion

The clinical signs, nature and distribution of lesions in these calves were sufficiently consistent to regard this syndrome as a distinct entity. The fortuitous presentation of calves at 1 day, 14 days, 19 days, 4 weeks, 5 weeks, 3 months, 4 months, 9 months, and 2 years of age, together with the clinical histories and appearance of light microscopic lesions, suggest progressive loss of spinal cord myelin with age. The light micro-
of the lesion occurs during the period of myelination which is between the 20th week of fetal life and 8 weeks after birth. The progressive nature of the disease after this period implies an innate inability of effective remyelination. The apparent late onset of signs in two calves (cases 8 and 9) may be explained by a mild expression of the disease neonatally. These animals inhabit large fields and are not closely observed. A mildly affected calf could easily have escaped detection until the stock were moved, yarmed, or in some other way closely examined. However, once neurologic signs were detected in these two cases subsequent regular observations confirmed the progressive nature of the disease.

The clinical signs and distribution of lesions within the central nervous system are similar in many respects to copper deficiency induced “delayed swayback” or enzootic ataxia of sheep. However, the lesions seen in copper deficiency probably originate in the axon and represent a primary axonopathy with secondary destruction of the myelin sheath although the pathogenesis may also involve abnormal myelin formation particularly at critical periods of central nervous system development.

There are several copper deficiency syndromes in cattle which are well documented, but a neurologic syndrome comparable to enzootic ataxia in sheep is rare in cattle. There are no comprehensive pathological studies. Sanders and Koestner described spongy change and paucity of myelin in the medulla oblongata of an ataxic calf considered to be copper deficient. However, only light microscopic observations were made, and the spinal cord was apparently not examined.

The copper concentration in the livers of four of our calves showed declining values with age: 295 ppm at 19 days of age, 80 ppm at 3 months, 5 ppm at 9 months, and 8 ppm at 2 years. The two older calves had liver copper stores in the deficient range (20–250 ppm is considered normal in local cattle by the Western Australian Department of Agriculture). Adequate levels in the two younger calves tend to discount copper deficiency as a possible cause. Additionally, four of the seven farms from which these calves derived had applied copper to pastures at recommended levels in recent years. The other three farms were under new management, and previous copper history was not available. However, the possibility that copper deficiency is a contributory factor in this disease cannot be rigidly excluded. Copper availability from pasture is influenced by relative levels of molybdenum and sulphur, and copper pasture applications may not be adequate in some circumstances. There is no evidence to suggest that copper is not as critical to the process of myelina
nation in cattle as it is in sheep in spite of the fact that neonatal ataxia in cattle is rare on copper deficient pastures. A further factor, or factors, may be involved in copper utilization during myelination in the bovine spinal cord.

The observation that copper concentration in the spinal cord of lambs with enzootic ataxia is lower than normal (J. McC. Howell, personal communication) prompted the determination of spinal cord copper concentration of case 3. Although we have no reference values for bovine spinal cord copper concentration, the figure of 2.82 ppm compared favorably with the 2.74 ppm recorded in a 9-day-old calf with liver disease submitted to the laboratory for routine diagnostic procedures. We include these results for possible future reference only.

It is pertinent here to make the comparison with enzootic ataxia in red deer (Cervus elaphus) kept in deer parks in which clinical signs and histopathologic lesions appear to be identical to our calves. Copper deficiency was considered the cause until recent investigations revealed that low copper intake and low liver copper stores were not associated with ataxia in a defined population of wild deer. Other wild ruminants including the llama (Lama glama), wildebeeste (Connochaetes taurinus), camel (Camelus dromedar-

Fig. 4. Advanced white matter degeneration in the ninth thoracic segment of a 2-year-old animal. The lesion is particularly severe in the peripheral aspects of ventral and lateral funiculi with relative sparing of dorsal funiculi. Luxol fast blue/periodic acid-Schiff.

ius) and fallow deer (Dama dama) may suffer a similar disease.

The microscopic appearance of affected spinal white matter in our calves is similar in some respects to the lesions present in hereditary neuraxial edema of Hereford calves, but the topographical distribution of lesions, breed specificity, and distinctive clinical signs are all markedly different.

A neurologic syndrome described in Hereford calves shares clinical similarities with our calves, and the brief description of the histopathological appearance of the spinal cord suggests a similar lesion may be present. However, these Hereford calves also had a suspected storage disease which affected neurons of the brain stem.

A hereditary hypomyelinogenesis congenita due to homozygosity of a simple autosomal recessive gene has been reported in Jersey, Shorthorn, Angus-Shorthorn and other breeds of cattle. The clinical signs, which in some calves were not apparent until 2 to 3 weeks of age, involve ataxia, incoordination, and tremors. The lesion appears to be associated with failure of myelin to develop rather than any destructive process.

A syndrome described in inbred horned Hereford cattle was associated with lesions in grey and white matter of the brain and spinal cord which consisted of
astrocyte swelling, intramyelinic vacuolation, and general paucity of myelin. The lesions, breed occurrence, and clinical signs were sufficiently different from the cases described in this paper to consider the two conditions as separate entities.

Intramyelinic vacuolation occurs in calves with experimentally induced hyperammonemia. However, the lesions are widespread in both grey and white matter of the brain and spinal cord. The lesion would only occur spontaneously in the presence of severe chronic hepatic disease.

A number of toxic conditions will produce central nervous system intramyelinic vacuolation experimentally in small laboratory mammals. These include Cu-prizone (biscyclohexanone oxaldihydrazone), hexachlorophene, acetyl ethyl tetramethyl tetralin, and triethyl tin. None of these compounds is likely to contaminate the environment of grazing beef cattle in Western Australia.

We conclude that the syndrome described here represents a primary defect in central nervous system myelin which selectively affects certain spinal white matter tracts resulting in progressive myelin loss with relative sparing of axons. A possible genetic predisposition in the Murray Grey breed of beef cattle is currently being investigated, and the results of breeding trials and further pathological studies will form the basis of a future publication.
Acknowledgements

The authors thank Dr. D. A. Purcell, Dr. C. R. Huxtable, Prof. J. McC. Howell, and Dr. R. M. Barlow for advice and Miss B. Jeanes for manuscript preparation.

References


Request reprints from Dr. R. B. Richards, Animal Health Laboratories, Department of Agriculture. Jarrah Road, South Perth, Western Australia, 6151.