Late Onset of Cerebellar Abiotrophy in a Holstein Heifer

F. Nguyen[1]*, C. George[2], A. Douart[3], Y. Cherel[1], F. Lars[4], M. Wyers[1]
[1]Department of Pathology, Veterinary School, BP 40706, 44307 Nantes cedex 03, France
[2]Pfizer Research Centre, ZI Pocé sur Cisse, BP 159, 37401 Amboise cedex, France
[3]Department of Large Animal Medicine, Veterinary School, BP 40706, 44307 Nantes cedex 03, France
[4]Veterinary Centre, 41 rue de Quimper, 29190 Pleyben, France
*Corresponding author (e-mail: fnguyen@sun.vet-nantes.fr)

KEY WORDS
Abiotrophy; bovine; cerebellum; genetic abnormality.

SUMMARY
A 22 month-old Holstein heifer presented with progressive signs of cerebellar dysfunction and emaciation of one-month duration, with gradual worsening. Gross and microscopic examination of the cerebellum was consistent with cerebellar abiotrophy, a condition characterized by premature death of Purkinje cells. The disease is supposed to be inherited in bovines; however in the present case, the onset of clinical signs was remarkably late.

INTRODUCTION
Cerebellar abiotrophy is a degenerative process characterized by premature degeneration and death of Purkinje cells of the cerebellar cortex[3,7] due to an intrinsic metabolic abnormality. The disease has been described in human, canine[8], feline[6], bovine, equine, porcine, simian and rodent species[7]. In cattle, many breeds[3] are affected, including Angus[1,5], Angus-cross[5,10], Charolais[2] and Holstein[4,9]. The present report describes a case of cerebellar abiotrophy in a Holstein heifer, aged 21 months when the first signs of ataxia occurred.

CASE HISTORY
A 22 month-old Holstein heifer was referred to the National Veterinary School of Nantes for progressive ataxia that began one month earlier in late summer. Physical examination revealed a wide-based stance and a symmetrical hypermetric gait affecting all four limbs. The animal was alert and responsive. Ten days prior to death, it was markedly emaciated and permanently recumbent, with normal vigilance. The heifer was euthanased by intravenous injection of sodium pentobarbital and immediately necropsied. Antigen detection of Bovine Virus Diarrhea virus (BVDV), performed on spleen and lymph nodes, was negative.

GROSS PATHOLOGY
The entire nervous system, including the cerebellum, was macroscopically normal. At necropsy, lymphoid organs appeared hyperplastic.

HISTOPATHOLOGY
Cerebrum, cerebellum, spinal cord, sciatic nerves, lymph nodes, spleen and a wide range of other organs were sampled for histological examination, fixed in 10% saline formalin, routinely embedded in paraffin wax, sectioned at 4 µm and stained with haematoxylin-eosin-saffron (HES). Klüver-Barrera staining was performed on nervous tissue.

Histopathological changes of the nervous system were confined to the cerebellum. At low magnification on each section, intact cerebellar folia were still present and randomly distributed. These few intact folia (Fig. 1A) displayed normal architecture and size. By comparison, most folia showed a homogeneous atrophy (Fig. 1B) due to a marked, multifocal to locally extensive, depletion of the granule cell layer, with molecular layer thinning.

At higher magnification, when compared to adjacent intact folia (Fig. 2A), a severe loss of granule cells and Purkinje neurons characterized the most affected areas (Fig. 2B). The thickness of both molecular and granular layers was dramatically reduced. Purkinje cells sometimes exhibited central chromatolysis, vacuolation or necrotic features with hypereosinophilia, cytoplasmic shrinkage and pyknosis. However, even in severely affected areas, distinction of the three layers of the cerebellar gray

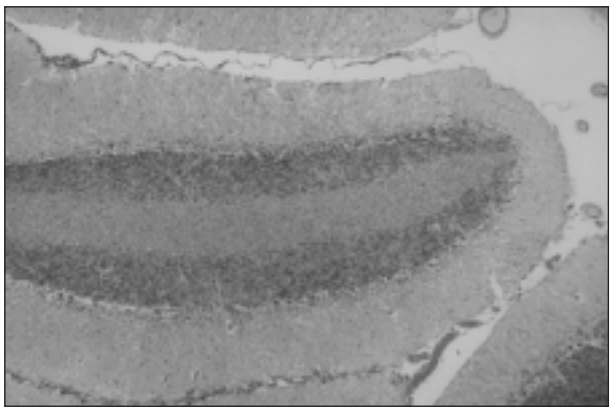

Figure 1A

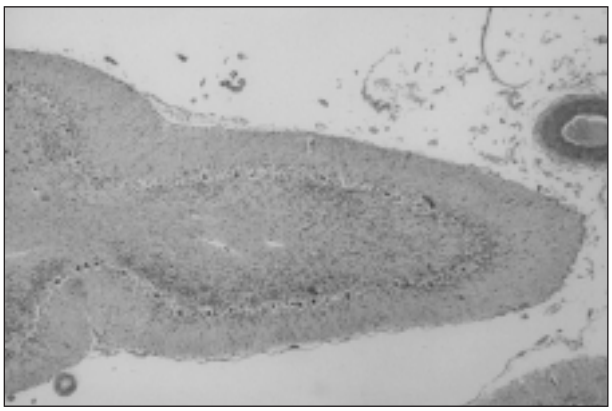

Figure 1B

Figure 1: Cerebellum, heifer, HES staining, x 40. (A) A few cerebellar folia are intact, with preserved architecture and thickness. (B) Adjacent and more numerous folia show a diffuse thinning of both the molecular and the granular layers of the grey matter, and a marked hypocellularity of the granule cell layer.

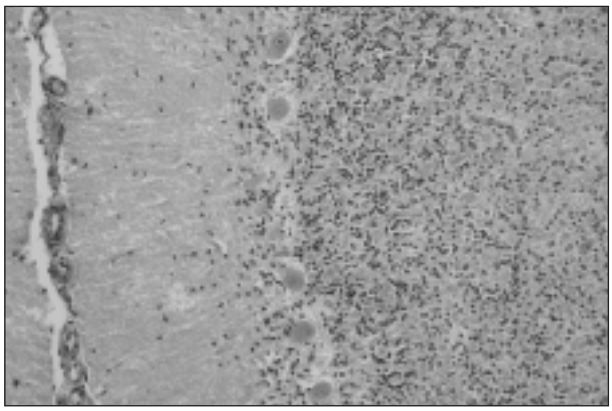

Figure 2A

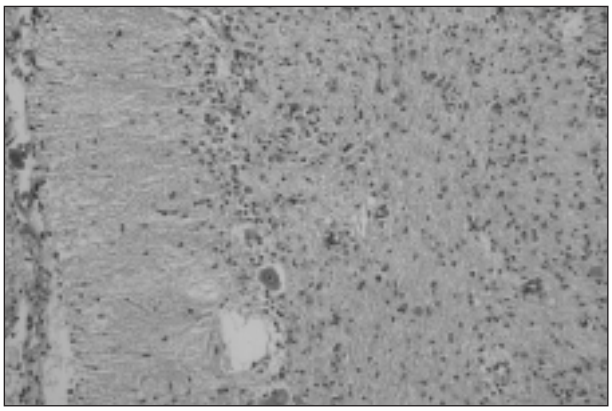

Figure 2B

Figure 2: Cerebellum, heifer, HES staining, x 160. (A) In intact folia, the molecular layer is thick and regular; the granule cell layer is highly cellular. (B) Adjacent folia are atrophied. Purkinje neurons are sparse and the granular layer is markedly depleted, two changes characteristic of cerebellar abiotrophy.

matter (molecular, Purkinje and granule cell layers) was always possible. Klüver-Barrera-stained sections of cerebellum revealed in white matter a few vacuolated myelin sheaths, suggestive of slight demyelination.

In lymph nodes, there was either a marked medullary plasmacytosis, or follicular hyperplasia with medullary histiocytosis and sinusoidal lymphocytosis. In the spleen a marked follicular hyperplasia was observed. These reactive changes were first considered to have resulted from infection with Bovine Immunodeficiency Virus (BIV), since this Lentivirus was prevalent in the herd of origin. However, the animal was serologically negative for BIV. No cause was found in this case for the reactive lymphoid hyperplasia.

DISCUSSION

Clinical signs (*i.e.* symmetrical hypermetric gait apparent several months after birth) and cerebellar microscopic lesions (presence of intact and affected folia, degeneration or absence of Purkinje cells, marked depletion of granule cells) supported a diagnosis of cerebellar abiotrophy. This disease is characterized by spontaneous premature degeneration of Purkinje cells due to an intrinsic unknown metabolic abnormality[1,3,7].

Cerebellar hypoplasia was ruled out because of the absence of macroscopic change, and the negative BVDV antigen assay. It usually occurs in newborn animals[7] and is characterized by different microscopic features (diffuse cerebellar atrophy due to failure of complete development, hypocellularity,

cavitation of the cerebellar white matter, ectopia of Purkinje cells and hypomyelination[7]).

The etiology and pathogenesis of cerebellar abiotrophy are poorly understood in calves, whereas in many breeds of dogs it is a congenital defect inherited as an autosomal recessive trait[3,7]. In Kerry blue terriers, the metabolic abnormality of Purkinje cells supposedly affects the glutamic acid neurotransmitter[3], causing cell degeneration by excitotoxicity. The loss of granule cells is considered to be a secondary phenomenon since their survival is dependent on synaptic relationships with Purkinje cells[3].

Previous reports of cerebellar abiotrophy in calves[2,3,4,9,10] suggested a genetic basis. In the herd of origin of the heifer, no other genetically related animal was similarly affected. However, at the period when clinical signs occurred in the heifer, an unrelated 16-month-old ox suffered from a similar, however transitory, cerebellar ataxia (of three-month duration). Full recovery from ataxia in calves with cerebellar abiotrophy has been described[1,4,10].

The first clinical signs of cerebellar abiotrophy in Holstein calves can appear at birth[4,10] or between three and eight months of age[2,5,9,10]. In the present case, onset of the disease was particularly late (21 months), although its clinical expression (gradual worsening of cerebellar ataxia leading to recumbency) was in agreement with previous reports[2,4,5,9,10] of cerebellar abiotrophy in cattle. Adult onset of cerebellar abiotrophy was reported in a cat[6], dogs[8] and Angus cattle[3]. Cerebellar abiotrophy is considered as a genetic abnormality of Purkinje cells in all affected species. Nevertheless, it is supposed that the electrophysiological disturbance of Purkinje neurons may remain clinically silent as long as compensatory synaptic changes occur[10].

Late onset of clinical signs in adults suggests a role for external factors enhancing neurotransmission derangement. In the present case, ingestion of perennial rye grass (*Lolium perenne*) pastured by the heifer was considered *a posteriori* as a possible triggering event. Perennial rye grass is responsible for transitory neurological signs in ruminants, in the absence of significant morphological changes, probably by inducing a functional neurotransmission defect[7]. Combination of a genetic background and plant intoxication could account for the late onset of cerebellar abiotrophy in the present heifer.

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