J. Comp. Path. 2015, Vol. 153, 135–139

Available online at www.sciencedirect.com

ScienceDirect

ELSEVIER

www.elsevier.com/locate/jcpa

SPONTANEOUSLY ARISING DISEASE

A Novel Inherited Cerebellar Abiotrophy in a Cohort of Related Goats

J. W. Koehler*, B. W. Newcomer*,†, M. Holland† and J. M. Caldwell†

** Department of Pathobiology and † Department of Clinical Sciences, College of Veterinary Medicine, Auburn University, Auburn, AL, USA*

Summary

Cerebellar abiotrophies, also known as cerebellar ataxias, are characterized by premature post-natal degeneration of cerebellar neurons. This report describes the clinical, magnetic resonance imaging (MRI), gross, histopathological and immunohistochemical features of a novel inherited cerebellar abiotrophy in a cohort of three closely related mixed-breed goats (*Capra aegagrus hircus*) in the southeastern USA. The animals all presented with early juvenile-onset ataxia, hypermetria, wide-based stance, head tremors and nystagmus. On MRI and at gross examination, there was moderate thinning of the cerebellar vermis and sharpening of the folia. Histologically, the vermis, paravermis and flocculonodular lobe had moderate to severe segmental loss of Purkinje cells with sparing of the hemispheres and secondary loss of granule cells and astrogliosis. Heritable cerebellar ataxias have been reported in many domestic animal species, but not, to the authors' knowledge, as a heritable condition in goats.

Keywords: animal model; cerebellar abiotrophy; cerebellar ataxia; goat

The term 'cerebellar abiotrophy' refers to a group of neurological diseases characterized by premature post-natal degeneration of cerebellar neurons secondary to defects in a variety of genes responsible for cellular metabolism and homeostasis (Summers *et al.*, 1995). In domestic animals, the condition is most often, but not always, inherited in an autosomal recessive fashion. Cerebellar abiotrophies known or suspected to be inherited have been reported in ruminants including cattle (White *et al.*, 1975; Whittington *et al.*, 1989; Mitchell *et al.*, 1993; Kemp *et al.*, 1995) and sheep (Harper *et al.*, 1986; Scott *et al.*, 1994; Milne and Schock, 1998; Johnstone *et al.*, 2005) and also in New World camelids (Mouser *et al.*, 2009). The disease in these species as well as in dogs, cats, horses and pigs is well-reviewed in several manuscripts and textbooks of veterinary neuropathology (de Lahunta, 1990; Summers *et al.*, 1995; Vandevelde *et al.*, 2012; Urkasemsin and Olby, 2014). Most cases in the literature are descriptive in nature, with a smaller number of reports investigating the genetic mapping or inheritance pattern in dogs (Urkasemsin and Olby, 2014) and Arabian horses (Brault *et al.*, 2011). Additional descriptions of clinically similar presentations of cerebellar ataxia acquired secondary to ingestion of various neurotoxic plants have been described in ruminants including goats (Bourke, 1997; Bourke *et al.*, 2008; Takeda *et al.*, 2014).

The onset of clinical signs in inherited cerebellar ataxias is variable, ranging from very early in post-natal life to late adulthood and signs are generally progressive early in the course of disease but may plateau. The lesions in affected human and veterinary patients relate to the primary cell type affected and the specific gene defect, but the most commonly described pattern in domestic animals is that of cerebellar cortical degeneration. The principle histopathologic change in these cases

Correspondence to: J. W. Koehler (e-mail: jaw0007@auburn.edu).

0021-9975/$ - see front matter
http://dx.doi.org/10.1016/j.jcpa.2015.06.001

is degeneration and loss of Purkinje cells, with secondary degeneration and loss of granule cells, thinning of the molecular layer, proliferation of Bergmann astrocytes in areas of Purkinje cell loss and in some cases formation of 'torpedoes' or axonal spheroids (Summers *et al.*, 1995; Vandevelde *et al.*, 2012). Evidence of trans-synaptic degeneration of neurons in cerebellar nuclei and/or retrograde degeneration of neurons in olivary nuclei are only described rarely in animals, once in a Labrador retriever dog (Bertalan *et al.*, 2014) and once in a domestic shorthair cat (Biolatti *et al.*, 2010).

In people, a comparable group of clinically similar, but genetically diverse, disorders is collectively referred to as the 'cerebellar ataxias', a designation that comprises at least 37 dominantly inherited diseases, 20 recessively inherited diseases and a small number of diseases that are known or suspected to be X-linked or mitochondrial in origin (Smeets and Verbeek, 2014). The present report describes the clinical, magnetic resonance imaging (MRI), gross, histopathological and immunohistochemical features of a novel inherited cerebellar abiotrophy in a cohort of closely related mixed-breed goats (*Capra aegagrus hircus*) in the southeastern USA.

All the goats were of mixed-breed and were from a small scale hobby farm in Alabama. Case 1 was a 9-month-old male and cases 2 (male) and 3 (female) were 6-month-old twins. All affected animals had the same sire and the two dams were both half-sisters to each other and second cousins to the sire. Of the seven kids born from the matings of the sire and these two dams, five have been affected and two unaffected; currently, two affected animals and two unaffected animals are alive. A mating between the sire and a third dam (also a half-sister to these dams by the same sire) has produced two unaffected offspring.

All goats were presented to the Auburn University Veterinary Teaching Hospital with a history of progressive clinical signs that began at approximately 2 months of age and included head bobbing/tremor, a wide-based stance, truncal ataxia and vertical to rotary nystagmus exacerbated by lateral or dorsal body positioning. In all cases, clinical signs appeared to worsen with excitement. Mentation was normal and no other neurological deficits or non-neurological signs were present. There was no history of exposure to known neurotoxins and the husbandry practices and geographical location of the farm did not support the idea of neurotoxic plant ingestion.

Haematological and serum biochemical parameters, including serum copper concentration, were within reference intervals and serum caprine arthritis and encephalitis virus titres were negative. Empirical treatment with thiamine, oxytetracycline, dexamethasone and sulphadimethoxine did not alleviate clinical signs. Cerebrospinal fluid from the lumbar cisterna of case 2 had mild blood contamination, but was otherwise normal and did not suggest an inflammatory or infectious process. MRI in a sagittal T1-weighted post-contrast image (case 3) showed an overall increase in cerebrospinal fluid (dark) around the cerebellum, with a diffuse decreased thickness and branching of the folia and increased fluid between the sulci and within the primary fissure (Supplementary Fig. 1). A diagnosis of cerebellar degeneration was made and the animals were humanely destroyed and submitted for necropsy examination.

On gross examination of the brain, there was mild thickening of the dura over the dorsal surface of the cerebellum and a mild subjectively increased amount of cerebrospinal fluid that exuded from the initial dural penetration. The volume of the cerebellum overall was mildly reduced, with noticeable narrowing of the width of the vermis and mild narrowing and sharpening of the folial profiles over the vermis and paravermal areas (Fig. 1).

The brain was fixed in 10% neutral buffered formalin. Serial coronal sections taken at approximately 5 mm to 1 cm intervals were processed routinely and embedded in paraffin wax. Sections (5 μm) were stained with haematoxylin and eosin (HE). Additional selected sections were subjected to immunohistochemistry (IHC) for detection of glial fibrillary acidic protein (GFAP; pre-diluted rabbit polyclonal anti-human FLEX; Dako, Carpinteria, California, USA) using an automated system (Autostainer Link, Dako) with a polymer-based horseradish peroxidase-conjugated detection kit with 3, 3′ diaminobenzidine tetrahydrochloride as the chromogen (EnVision™ FLEX high-pH kit, Dako). Antigen retrieval was performed by heating in citrate buffer (pH 6.1) and quenching of endogenous peroxidase activity was via immersion in a phosphate buffer containing H_2O_2, 15 mmol/l NaN_3 and detergent (EnVision™ FLEX Peroxidase-blocking Reagent, Dako). Slides were counterstained with haematoxylin. Unaffected areas of the cerebellum were used as positive internal controls. For negative reagent controls, slides in which the step of incubation of the primary antibody was removed from the protocol were used. Negative internal tissue controls in immunolabelled slides consisted of non-glial tissue elements such as blood vessels, neurons and meningeal tissues, which did not demonstrate any immunoreactivity for GFAP.

Subgrossly, in the vermis, paravermal and flocculonodular areas there was marked reduction in the density of the internal granule cell layer, a mild decrease