CASE REPORT

# Cerebellar cortical abiotrophy in Lagotto Romagnolo dogs

**This case report documents two pathological variations of potentially inherited, cerebellar cortical abiotrophy in two unrelated Lagotto Romagnolo breed dogs. The first dog had an atypical lesion in the cerebellar cortex with depletion of cerebellar granular cell layer and sparing of the Purkinje cell layer. The second case had degenerative changes in both Purkinje and granular cell layers. The clinical picture was similar in both cases presented, although the severity of the signs of cerebellar dysfunction varied.**

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## INTRODUCTION

Abiotrophy is a term used to describe premature tissue degeneration typically because of an intrinsic abnormality in the cell's structure, altering metabolic processes necessary for cell vitality and function (deLahunta 1990). One of the more common abiotrophies in domestic animals are those affecting the cerebellar cortex (Summers and others 1994). Typically, the predominant histological lesion is loss or degeneration of Purkinje cells, with or without granular cell loss. Cerebellar cortical abiotrophy has been reported in many dog breeds, for example in Kerry blue terriers, Gordon setters, Australian kelpies, Brittany spaniels, Rhodesian ridgebacks, Old English sheepdogs, Coton de Tuléar dogs, beagles, Portuguese podencos, Scottish terriers, border collies, miniature schnauzers, Staffordshire terriers and English bulldogs (deLahunta and Averill 1976, Steinberg and others 1981, Thomas and Robertson 1989, Tatalick and others 1993, Chieffo and others 1994, Kent and others 2000, Steinberg and others 2000, Tipold and others 2000, van Tongeren and others 2000, van der Merwe and Lane 2001, Sandy and others 2002, Berry and Blas-Machado 2003, Speciale and deLahunta 2003, Gandini and others 2005). The age of onset and the progression of signs of cerebellar dysfunction vary markedly according to the breed affected, and the histological picture is similar in affected dogs representing the same breed.

This is, to the authors' knowledge, the first case report of cerebellar cortical abiotrophy in an ancient Italian dog breed the Lagotto Romagnolo. Cerebellar granuloprival degeneration has been reported in an Italian hound, but unfortunately, the breed of the dog was not mentioned (Cantile and others 2002). Both cases presented here were young Lagotto Romagnolo breed dogs. Unusually, there were two different pathological variations: one of the dogs had severe depletion of the granular cell layer only and the second dog had depletion of the Purkinje cell layer with degenerative changes also in the granular cell layer.

## CASE HISTORIES

### Case 1

A 15-week-old, female Lagotto Romagnolo dog was presented to the Small Animal Hospital of the University of Helsinki for evaluation of an abnormal gait. The owner had been aware of an ataxic pelvic limb gait since the puppy was 13 weeks old. The signs had been progressive. The owner also described a head tremor when the dog was eating or exploring. The dog was dewormed several times with fenbendazole (Axilur; Intervet) and was vaccinated at the age of 12 weeks against parvovirus, distemper virus, canine adenovirus 2 and canine parainfluenza (Nobivac DHPPi vet; Intervet). The blood biochemistry profile (electrolytes, total protein, albumin, cholesterol, creatinine, urea, total and conjugated bilirubin, alanine aminotransferase, alkaline phosphatase, bile acids) and complete blood cell count were established to be within the normal limits by the referring veterinarian. All seven puppies of this litter had been normal at birth. The general physical examination of the puppy was normal. The dog was bright and alert. On neurological examination, the dog had generalised ataxia (all four limbs, trunk and head) with thoracic limb hypermetria. There was mildly decreased proprioception in all four limbs. The spinal reflexes were normal. The menace response was decreased on both eyes, but vision and other cranial nerves were normal. Based on the findings of the neurological

examination, the lesion was localised to the cerebellum. The differential diagnoses included cerebellar malformation (hypoplasia), abiotrophy, inflammatory or infectious conditions, storage diseases and neoplasia. Magnetic resonance imaging (MRI) was performed with 1·5 T MRI machine (Siemens Symphony 1·5 T). Routine T1-weighted and T2-weighted sequences in sagittal, transverse and dorsal planes were obtained (3 mm slice thickness). The cerebellum was mildly decreased in size; this was especially apparent in the sagittal sections. On T2-weighted images, the cerebellar folia appeared narrowed, and sulci were widened. There was no enhancement after gadolinium administration (469 mg/ml Magnevist; Schering AG) (0·1 mmol/kg). The results of cerebrospinal fluid examination, collected by cisternal puncture, were normal (protein content and cell count).

The owner requested euthanasia of the dog at the age of 17 weeks because of the rapid progression and severe nature of the clinical signs. The only gross post-mortem examination finding was a small cerebellum, which weighed only 7 per cent of the total brain weight (4·75 g of 63·98 g; normal, >10 per cent [Summers and others 1994]). The histological examination showed a clear loss of neurons in the cerebellar granular cell layer (Fig 1). The amount and localisation of the Purkinje cells and the molecular layer were normal. In addition, scattered small foci of perivascular lymphocytes were seen in the cerebellar white and grey matter. No pathological changes were seen in other parts of the central nervous system. The only additional histological finding was a mild, acute, diffuse interstitial pneumonia with intracytoplasmatic eosinophilic inclusions in the bronchial epithelium and generalised hyperplasia of lymphatic tissues. The lung findings in combination with the generalised lymphatic hyperplasia were interpreted as vaccine-induced changes because the puppy had just been revaccinated against canine distemper virus. Based on the history and pathological findings, an abiotrophy of the cerebellar cortical granular cell layer was diagnosed. An immunohistochemical staining for parvoviral antigen and PCR (Cornell University, Ithaca, NY) of cerebellar tissue for parvoviral DNA were performed to exclude a possible viral aetiology for the changes. The results were negative. To assess the nature of the sparse inflammatory reaction seen in the cerebellum, an immunohistochemical staining for T- and B-cell receptors (CD3, CD79a) was done. The majority of the sparse lymphocytes occasionally cuffing small vessels of the cerebellum were CD3 positive, interpreted as T cells.

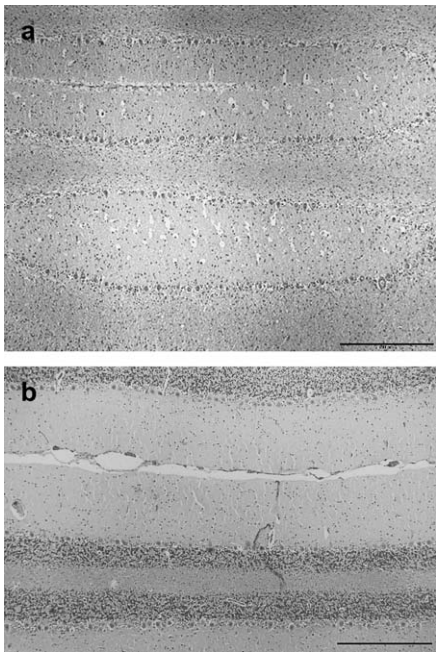


**FIG 1. Photomicrographs of a section of cerebellar vermis, stained with haematoxylin and eosin, from an affected (a) and normal (b) dog (magnification ×4). Note the severe depletion of the granular cell layer and sparing of Purkinje cells in the affected dog. Scale bar represents 500 μm**

## Case 2

A 10-week-old, female Lagotto Romagnolo was presented to the Department for Small Animals, at the University of Zurich. The breeder of this puppy reported ataxia, loss of balance and occasional falling since the age of five weeks. The clinical signs were initially progressive until the age of eight weeks and then persisted without worsening of signs. Otherwise the puppy was behaving normally. The puppy was unvaccinated and had never received deworming medication. Littermates of the puppy were normal. The general physical examination of the puppy was normal. On neurological examination, the dog had normal mental status. It exhibited a broad-based stance and obvious generalised ataxia. Intention tremor was present when the dog was drinking or eating. The spinal reflexes were normal. Proprioception was moderately decreased in all four limbs. The menace response was decreased on both eyes, but other cranial nerves were normal. Based on the neurological examination findings, the lesion was localised to the cerebellum. In blood cell count, there was a moderate leucocytosis ($15{\cdot}8\times10^9$/l; range 4·7 to 11·3) with mature neutrophilia ($11{\cdot}22\times10^9$/l; range 2·49 to 7·44). The blood biochemistry profile (electrolytes, total protein, albumin, cholesterol, creatinine, urea, alanine aminotransferase, alkaline phosphatase, bile acids) was within normal limits. There were no abnormal changes in the brainstem auditory evoked response test. MRI was performed with 1·5 T MRI machine. Routine T1-weighted and T2-weighted sequences in sagittal and transversal planes were obtained. No abnormalities were noticed, and there was no enhancement after gadolinium administration. The protein content and cell count in the cerebrospinal fluid, collected by cisternal puncture, were normal.

The dog was euthanased at the owner's request at the age of 10 weeks, and a pathological examination was performed. There were no gross post-mortem examination findings. Histologically, there was broadening of sulci and depletion of the Purkinje cell layer with reactive astroglial proliferation (Fig 2). Degenerative changes were seen in the granular cell layer. All described changes were visible throughout the cerebellar cortex. In addition, there was vacuolisation of the cerebellar white matter. There were no abnormalities found in rest of the central nervous system or in any other body organs. A diagnosis of cerebellar abiotrophy was made based on the histological findings.

## DISCUSSION

Animals with cerebellar abiotrophy are usually neurologically normal at birth and later develop progressive signs of cerebellar disease. The dog's age when signs of cerebellar disease are first recognised

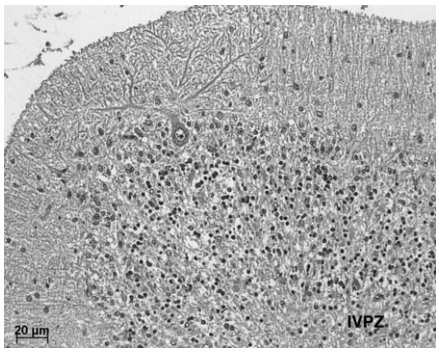


**FIG 2. Photomicrograph of a section of cerebellum, stained with haematoxylin and eosin, from a dog with severe depletion of Purkinje cell layer with degenerative changes also in the granular cell layer. Scale bar represents 20 µm. Institut für Veterinar Pathologie Zurich (IVPZ)**

seems to vary according to the breed affected from a few weeks (Thomas and Robertson 1989, Chieffo and others 1994, Kent and others 2000, van Tongeren and others 2000) to months (Steinberg and others 1981, Tipold and others 2000, van der Merwe and Lane 2001, Cantile and others 2002, Sandy and others 2002, Berry and Blas-Machado 2003, Gandini and others 2005) or in some cases, even years (Tatalick and others 1993, Steinberg and others 2000, Speciale and deLahunta 2003, Olby and others 2004). Both cases presented here represent an early onset of cerebellar dysfunction. In addition, the speed of progression varies with the breed affected. The signs of cerebellar dysfunction have been reported to progress rapidly during weeks (Chieffo and others 1994, Tipold and others 2000, van Tongeren and others 2000, Berry and Blas-Machado 2003) or more slowly during months (Tatalick and others 1993, Kent and others 2000, Cantile and others 2002, Sandy and others 2002, Gandini and others 2005) or years (Steinberg and others 2000, van der Merwe and Lane 2001, Speciale and deLahunta 2003, Olby and others 2004). In case 1, the signs of cerebellar dysfunction progressed rapidly during weeks, and in case 2, after initial progression of signs, the status was stable.

The most obvious histopathological finding in reported cases of cerebellar cortical abiotrophy has usually been depletion of Purkinje cells (Steinberg and others 1981, Thomas and Robertson 1989, Chieffo and others 1994, Summers and others 1994, Kent and others 2000, Steinberg and others 2000, van Tongeren and others 2000, van der Merwe and Lane 2001, Berry and Blas-Machado 2003, Speciale and deLahunta 2003, Olby and others 2004). Furthermore, in the previously reported cases of cerebellar abiotrophy, the histological picture has been similar for dogs of the same breed. We found two different histological variations of cerebellar cortical degeneration in one dog breed. In case 1, there was extensive loss of granular cells but with normal amount of Purkinje cells. Abiotrophy of the granular cell layer is a rarely encountered form of inherited cerebellar cortical degeneration (Tatalick and others 1993, Tipold and others 2000, Cantile and others 2002, Sandy and others 2002). Primary depletion of the granular cell layer has also been reported in Brittany spaniels (Tatalick and others 1993), in Coton de Tuléar dogs (Tipold and others 2000), in an Italian hound (Cantile and others 2002) and in border collies (Sandy and others 2002). In case 2, both Purkinje and granular cell layers were affected. This has been the case also in some other dog breeds with cerebellar cortical degeneration (Steinberg and others 1981, Thomas and Robertson 1989, Steinberg and others 2000, Speciale and deLahunta 2003, Gandini and others 2005).

Cerebellar abiotrophy is diagnosed when an exogenous cause cannot be found to explain the cortical cerebellar cell degenerative changes. Different theories for cerebellar degeneration include excitotoxic degeneration of neurons with glutamate receptors, including Purkinje cells (Montgomery and Storts 1984, deLahunta 1990), channelopathies with abnormal structure and function of voltage-gated calcium channels (Frontali 2001) and autoantibody-mediated disorders which have been recently reviewed in human beings (Lang and others 2003). Other theories have been proposed to explain the degeneration of certain cerebellar cortical cells. Granule cell neurons are formed from the external germinal cell layer later in gestation than Purkinje neurons, and their formation is completed postnatally during cerebellar development (deLahunta 1983). Whether primary granular or Purkinje cell depletion occurs in different cases of cerebellar abiotrophy may be because of the difference in migration times of these two cell populations. The reason for the selective depletion of granular cells still needs to be clarified. In Coton de Tuléar dogs, a genetically defined immune defect leading to autoimmune destruction of granular cells was suggested (Tipold and others 2000). A similar kind of immune-mediated destruction of the granular cell layer could be suspected in case 1.

In utero or perinatal infection of the brain with feline panleukopenia virus causes destruction of the external germinal layer, causing hypoplasia of the granular cell layer in cats (deLahunta 1983). There is no proof that a similar process occurs in canine parvovirus infections, but it has been suggested that cerebellar hypoplasia in dogs might be associated with in utero parvoviral infections (Schatzberg and others 2003). PCR for brain parvoviral DNA was negative in case 1. This is consistent with the findings of a study in which parvoviral DNA was amplified with PCR from the brain of eight cats and two dogs with cerebellar hypoplasia but not from two dogs with cerebellar cortical abiotrophy (Schatzberg and others 2003).

## Conclusions

Based on the history and histological degenerative changes in the cerebellar cortex, and in the absence of an exogenous cause, two different variations of cerebellar cortical abiotrophy were diagnosed in two Lagotto Romagnolo dogs. The mode of inheritance remains to be proven as well as the role of the immune system in the disease process.

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