Short communication

Spongiform leukoencephalomyelopathy in Border Terriers: clinical, electrophysiological and imaging features

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A novel spongiform leukoencephalomyelopathy was reported in Border terrier puppies in 2012 causing a shaking puppy phenotype, but no information regarding clinical progression, imaging or electrophysiological findings were available. The aim of the present study was to describe the clinical, electrophysiological and magnetic resonance imaging (MRI) features of this disease in seven dogs and compare them with human white matter disorders. All cases presented with cerebellar ataxia and severe generalised coarse body tremors, which started at 3 weeks of age. The three cases that were not euthanised showed slow but progressive improvement over several months. Brainstem auditory evoked response demonstrated a normal wave I, reduced amplitude of wave II and an absence of waves III to VII. Magnetic resonance imaging revealed bilateral and symmetrical T2-weighted hyperintensities affecting the brainstem and cerebellar white matter. Histologic examination of the brain and spinal cord showed spongiform change affecting the white matter of the cerebellum, brainstem and spinal cord with decreased myelin content. In summary, this leukoencephalomyelopathy has a pathognomonic clinical presentation with defining MRI and electrophysiological characteristics and this is the first report to describe a long-term improvement of this condition.

Keywords: White matter disorder; Leukodystrophy; Dog; Magnetic resonance imaging

White matter disorders or leukoencephalopathies include disorders that predominantly affect the white matter of the brain.[1] Leukodystrophies are heritable disorders affecting the white matter of the central nervous system with or without peripheral nervous system involvement.[2] In demyelinating leukodystrophies, there is production of defective myelin that cannot be maintained, and in hypomyelinating leukodystrophies there is a decreased myelin production.[1] In the past the majority of leukodystrophies remained without a specific diagnosis. Magnetic resonance imaging (MRI) pattern recognition has proven to be pivotal in the diagnosis of human leukodystrophies, as individual leukoencephalopathies show distinct patterns and intensity changes on MRI, which are homogeneous among patients with the same disorder.[3]

In veterinary medicine, there are reports of hypomyelinating and demyelinating leukodystrophies affecting multiple dog breeds, but very little is known about their MRI characteristics.[4-15] In 2012, Martin-Vaquero et al.[9] reported a novel leukoencephalomyelopathy with spongy degeneration and hypomyelination in Border terrier puppies, but no information regarding the clinical progression, MRI and electrophysiological findings have been reported. Recently, a genetic test has become available, but no information regarding the gene involved has been published at the time of writing this short communication.[16]

The aim of this study was to describe the clinical, electrophysiological and MRI features of this newly reported canine leukoencephalomyelopathy and compare them with human white matter disorders.

Seven Border terrier puppies (6 males and one female) from 4 different and unrelated litters were presented to two referral hospitals. In all cases the rest of the littermates and both parents were reported to be completely normal. For one of the litters the owners had been weighing the puppies since birth, and despite not showing any clinical signs at birth the 2 affected

puppies weighed 40% less than the other littermates and remained smaller weighing 65% less at one month of age. In all cases the owners reported generalised coarse body tremors that started at around 3 weeks of age. The tremors continued progressing and all the puppies had to be helped to eat. All affected puppies presented for examination at around 6 weeks of age and physical examination was unremarkable. Neurological examination showed normal mentation and cranial nerves examination except from bilateral absent menace response, which was considered a normal finding for their age. Severe and generalised coarse body intention tremors were observed in all puppies. Tremors were more severe in the pelvic limbs and stopped when the dogs were asleep or at rest (video 1; supplementary material). Hypermetria of the pelvic limbs was evident when the puppies tried to walk. Paw positioning was normal and hopping was delayed on the pelvic limbs. Segmental spinal reflexes were normal and there was no pain on palpation of the vertebral column. Due to the characteristics of the tremors a diffuse process affecting the myelin was considered the main differential diagnosis.[17] Six of the puppies were tested for the recently identified genetic mutation and were homozygous mutant.

No further evaluation was performed on three dogs. They all showed gradual deterioration until four months of age, and then started improving and by one year of age they exhibited just mild tremors (videos 2 and 3; supplementary material). Two of the puppies are still alive and doing well, but the other one developed seizures at 2 years of age and was euthanised with no post-mortem examination performed.

Of the remaining four dogs, two were euthanised after examination and serum biochemistry, electrophysiological and imaging studies were performed on the other two. Haematology, biochemistry, ammonia and blood lactate levels were unremarkable. Brainstem auditory evoked response (BAER) showed bilaterally normal wave I, reduce amplitude of wave II and absence of waves III to VII (Fig. 1). Magnetic resonance imaging (MRI) of the brain was

performed with a 1.5T magnet (Magnetom, Siemens, Camberley, United Kingdom). All lesions were compared with the intensity of normal grey matter. There were small multifocal T2-weighted hyperintensities in the cerebral white matter and marked bilateral symmetrical hyperintensities in the mesencephalus, pons, medulla oblongata and cerebellar white matter. All the lesions were mildly hyper-to isointense in FLAIR images, iso- to hypointense on T1-weighted images and did not show contrast enhancement after intravenous gadolinium administration (0.1mmol/kg; Gadovist, Bayer plc) (Fig. 2). It was also noticed that the caudal part of the corpus callosum was very thin (Fig. 1). Cisternal cerebrospinal fluid examination was unremarkable, except for moderate increase in lactate levels (3.2 and 3.9mmol/l, ref: 1.02-2.49).[18] The owner of these two puppies elected for euthanasia after investigations.

Post-mortem examination was performed in these four puppies. No macroscopic changes were observed. The only significant histopathological changes were present in the brain and spinal cord with normal myelination of the peripheral nervous system. The changes were very similar to the ones described by Martin-Vaquero et al.[9] characterised by marked vacuolation (spongiform degeneration) of the white matter of the spinal cord, cerebellum and caudal brainstem with milder changes in the thalamus and cerebral white matter. Decreased myelin content was evident with luxol fast blue staining (Fig 2). There was also a moderate to diffuse increase in the number of glial cells and neuronal somas were unremarkable.

The present study is the first to report that at least some of the puppies affected by this disease could show gradual improvement of the clinical signs after 4 months of age. This is also the case in some human, mouse and canine leukodystrophies, as there can be remyelination or delayed myelination.[11,19,20] Interestingly, weight at birth of the affected puppies was much lower than the littermates, suggesting that the disease process could have been affecting them even before birth. Recent studies in dogs, suggest that weight at birth is related to neonatal welfare,

morbidity and mortality.[21,22] Seizures have been reported in canine and human leukodystrophies, and were observed in one of the puppies that had shown initially a gradual improvement.[14,23] Unfortunately, no post-mortem examination or genetic test were performed in this case, so we are not able to confirm if they were secondary to the leukoencephalomyelopathy.

The BAER findings of the present cases are compatible with central involvement (brainstem myelination disorder), but no peripheral nerve (cranial nerve VIII) involvement, as wave I latency and amplitude were normal. BAER have been reported to be useful in detecting peripheral and central involvement in myelination disorders in humans, and it could represent a useful and inexpensive test in puppies with a "shaking" phenotype.[24]

In humans, systematic review of MRI patterns has proven to be a practical and helpful approach for diagnosis white matter disorders.[1,3] As white matter is myelinated, it changes from hypointense to hyperintense relative to gray matter on T1-weighted and from hyperintense to hypointense relative to gray matter on T2 weighted.[25] If we follow the human MRI-based approach for diagnosis of white matter disorders, the present cases will be in the group of other white matter pathologies, as they show prominent T2-weighted hyperintensity and T1-weighted hypointensity.[1,3] Then, the fact that the white matter abnormalities are confluent and bilateral, and that the major preferential localisation of the abnormalities is the caudal cranial fossa (affecting the brainstem and cerebellar white matter) would make a peroxisomal disorder, Alexander disease or a mitochondrial disorder more likely.[3] Very similar MRI distribution pattern to the one seen in the present cases have been reported in some human mitochondrial disorders, such as leukoencephalopathy with thalamus and brainstem involvement and high lactate and leukoencephalopathy with brainstem and spinal cord involvement and increased lactate concentration.[20,26] Interestingly the lactate concentrations in CSF were increased in the

two puppies where CSF was taken, and it was also increased in the urine of a previously reported case.[9] Increase lactate is a common finding in mitochondrial disorders.[27]

In conclusion, some Border terriers with a shaking puppy phenotype can show gradual improvement of the clinical signs, and MRI and BAER can be useful to further characterise white matter disorders in dogs.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix A: Supplementary material

Video 1: Two 4-week-old affected Border terrier puppies with the characteristic tremors and ataxia.

Videos 2: Short-term follow up of one affected Border terrier puppy from 6 weeks until 9 weeks of age. Notice how the affected puppy is significantly smaller than the litter mates and showing serve ataxia and tremors.

Videos 3: Long-term follow up of 2 affected Border terrier dogs from 8 weeks until 5 years of age. Notice the significant improvement of the clinical signs over time.

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Figure legends

Fig. 1. Brainstem auditory evoked response of an affected Border terrier puppy (A) and a normal puppy of the same age (C). Notice that wave I is normal, wave II has a reduce amplitude and waves III-VII are absent. Sagittal T2 weighted MRI image of an affected Border terrier puppy (B) and a normal puppy of similar age (D). Notice the T2-weighted hyperintensities in the brainstem and cerebellar white matter (white arrows) and the thinning of the caudal part of the corpus callosum (black arrows).

Fig. 2. Transverse views at the level of the fourth ventricle of an affected 6 week- old Border terrier puppy. MRI: T2-weighted (A), FLAIR (B), T1-weighted before (C) and after contrast (D). Histopathology: haematoxylin-eosin (E) and luxol fast blue (F). Notice the T2-weighted hyperintensity, T1-weighted hypointensity and vacuolation affecting the cerebellar and brainstem white matter (asterisks).