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Cerebellar ataxia in a young dog.

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What's your neurological diagnosis? Cerebellar ataxia in a young dog

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History:

A 4-year-old spayed female American Staffordshire terrier mix was presented for a multiple week history of progressive ataxia and collapsing episodes. Approximatively 2 weeks prior to presentation, the owner reported she started slightly dragging her pelvic limbs and kicking up grass as she ran. By one week prior to presentation, she was reportedly swaying when walking and collapsing after running about 20 feet. The patient was current on vaccinations with an otherwise unremarkable medical history.

On presentation, the patient's general physical examination was unremarkable. The patient appeared to experience episodes of collapse during activity but, after resting for short periods, recovered uneventfully (see supplemental video). At presentation, a neurological examination was performed.

*****NEURO EXAM- SEE PDF*****

Formulate your anatomic and etiologic diagnoses, then continue reading.

Assessment:

Anatomic Diagnosis:

In this dog, the collapse after short periods of activity could be suggestive of a neuromuscular condition. However, tetraparesis or systemic weakness were not consistently seen, making this less likely. Collapse could also occur due to a loss of balance from vestibular or cerebellar disease and may coincide with leaning, falling or a wide based stance. In this case, the collapse was noted to occur with sudden movements of the head. Additionally, the intermittent hypermetria, ataxia and swaying of the head, neck and trunk suggests a cerebellovestibular ataxia, consistent with a cerebellar lesion.

Likely Location of the Lesions:

The cerebellum was considered the most likely location of the lesion.

Etiologic Diagnosis:

Differential diagnoses for progressive cerebellar disease included autoimmune (meningoencephalitis of unknown etiology [MUE]) or infectious (bacterial encephalitis, fungal encephalitis [*Cryptococcus neoformans* or *Coccidioides immitis*], viral encephalitis [canine distemper virus or rabies virus], or parasitic [*Toxoplasma gondii* or *Neospora caninum*] infection) diseases. Given the patient's age, neoplastic diseases (such as medulloblastoma and lymphoma), and degenerative diseases (such as cerebellar cortical degeneration of American Staffordshire terriers) were considered. Acquired myasthenia gravis was considered unlikely but could not be completely ruled out as a potential concurrent disease, to explain the episodes of exercise-related collapse.

Diagnostic Test Findings:

Clinicopathologic analyses [complete blood count (CBC), serum biochemical analyses including creatine kinase levels], as well as thoracic radiographs were performed, and were all within normal limits. Serum acetylcholine receptor antibody titers were sent out for quantification. Magnetic resonance imaging (MRI) of the brain and cervical spinal cord was performed using a high-field MRI (3T; Philips). Sagittal (Figure 1) and transverse T2-weighted (T2W) images as well as sagittal, transverse, and dorsal T1-weighted (T1W) images (before and after gadolinium contrast administration) were obtained. Transverse images were also acquired using T2* gradient recalled echo, T2W fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) map sequences. MRI revealed diffuse

cerebellar cortical atrophy (Figure 1). Based on the MRI findings, the top differential was cerebellar cortical degeneration of American Staffordshire Terriers. Blood was submitted for genetic testing. To further rule out other causes, cerebrospinal fluid (CSF) was collected from the cerebellomedullary cistern and was normal. On recovery from anesthesia, a transient spontaneous horizontal nystagmus was appreciated. The patient was discharged the following day to the owners' care with plans to monitor for signs of progression.

Acetylcholine receptor antibody titers were later confirmed to be normal at a concentration of 0.01 nmol/L (ref: <0.6 nmol/L), further helping rule out myasthenia gravis. Genetic testing for cerebellar cortical degeneration of American Staffordshire terriers confirmed the patient had two mutant copies of the *ARSG* gene. The patient was euthanized two months following diagnosis due to progressively worsening cerebellar dysfunction such that the patient could minimally ambulate at time of euthanasia. Necropsy was performed and histopathology confirmed cerebellar cortical atrophy with loss of Purkinje neurons and hypocellularity within the granule cell layer (Figure 2). Pigment accumulation was identified within the remaining Purkinje neurons and stained positive on Periodic Acid Schiff stain (Figure 2). These findings were consistent with the degenerative lysosomal storage disorder, cerebellar cortical degeneration of American Staffordshire Terriers.

Comments:

Lysosomal storage disorders are neurodegenerative, autosomal recessive disorders where a patient is deficient in specific enzymes associated with lysosomal catabolic pathways.[1, 2] This leads to accumulation of various toxic materials within neurons, with cerebellar Purkinje neurons being especially sensitive, due to their high metabolic demands.[2, 5] Clinical signs often

present in young animals less than 6 months of age but select conditions in specific breeds have been associated with a later onset of signs.[5]

American Staffordshire terriers experience a late-onset lysosomal storage disorder secondary to a mutation of the *ARSG* gene.[1,2] This condition was originally called cerebellar cortical degeneration of American Staffordshire terriers, and is colloquially known as cerebellar abiotrophy or cerebellar ataxia; however, it since has been reclassified several times.[1,2,4,5] Initially, it was thought to be a form of neuronal ceroid lipofuscinosis, and was termed NCL-4A.[1] However, recent research with *ARSG* knock-out mice has suggested that this disease is a type of mucopolysaccharidosis.[4] Due to the multiple reclassifications and continued research on this disorder, the terminology throughout the literature remains inconsistent. However, it is important to consider this condition when working with juvenile to older aged American Staffordshire terriers with progressive cerebellar disease.

In American Staffordshire terriers with this disease, the age of onset of clinical signs has been reported to vary from 18 months to 9 years with the majority of patients developing neurological signs between the ages of 4 – 6 years.[5] Most commonly these patients are initially identified by owners as stumbling especially when attempting to navigate stairs, corners, hills, and jumping up onto objects.[5] They may also display mild sway of the head, neck and trunk, intermittent recumbency with opisthotonus or full body jerks, and stiffening during sleep.[5] As signs progress, they display thoracic and/or pelvic limb hypermetria, a wide-based stance, truncal sway, falls when moving or shaking their heads, and markedly worsening signs with sudden movements and excitement due to overcompensation.[5] Some patients also develop spontaneous or positional nystagmus or an intermittent head tilt.[5] Most notably patients have

an otherwise unremarkable cranial nerve examination, no conscious proprioceptive deficits, and appear normal when walked in a straight line without sharp movements or inclines.[5] MRI findings reveal generalized cerebellar cortical atrophy with increased cerebrospinal fluid between the folia of the cerebellum.[5] Cerebrospinal fluid analysis is classically unremarkable and histopathology reveals marked loss of Purkinje neurons within the cerebellum.[5] A strong clinical suspicion and working diagnosis can be made based on MRI findings and genetic testing ante-mortem.[3] Unfortunately, there is no treatment available at this time, and patients with this disorder are usually euthanized within 6 months to 6.5 years due to loss of the ability to ambulate.[5]

In this report, neurolocalization based on examination findings was made to the cerebellum due to the intermittent hypermetria, generalized cerebellovestibular ataxia, and sway of the head, neck, and trunk. As the patient was seen to collapse during activity, initially neuromuscular disease such as myasthenia gravis was also considered. However, with further careful gait examination outdoors, the amount of activity prior to collapse was variable and collapse was consistently seen following sudden head and neck movements (see supplemental video). In some instances of cerebellar disease, dysregulation of the vestibular and cerebellar systems can occur, resulting in loss of balance and overcompensation, especially with sudden turns or movements of the head. This may cause collapse or recumbency with or without opisthotonos, as seen in the patient in this report. A thorough neurological examination, including gait assessment in various environments, such as up and down inclines, or walking with the head raised, can be helpful in further differentiating collapse due to cerebellar dysfunction from exercise-induced weakness due to neuromuscular disease and other causes.

This report highlights the presentation and diagnosis of a relatively common lysosomal storage disorder, as well as the importance of a thorough neurological examination and diagnostic work-up, including genetic testing.

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JAVMA What Is Your Neurologic Diagnosis?
Neurologic Examination Form

Observation

Mental	Alert	X	Depressed		Disoriented		Stupor		Coma		
Posture	Normal	X	Head tilt		Tremor		Falling	X	Other	X	
Gait	Normal		Ataxia	X	Pelvic limbs		All 4	X	Circling		
Paresis	Pelvic limb		Tetra		Hemi		Mono				
Other	Normal posture at rest. Generalized ataxia and sway involving all limbs, head and neck. Intermittent thoracic limb hypermetria. When made to walk or run, the patient would frequently collapse in all limbs after 2-3 minutes of activity, with no change in mentation.										

Key: 4 = Exaggerated, clonus, 3 = Exaggerated, 2 = Normal, 1 = Diminished; 0 = None; NE = Not evaluated.

Postural reactions

	Left forelimb	Right forelimb	Left hind limb	Right hind limb
Wheelbarrow	NE	NE		
Hopping	2	2	2	2
Extensor postural thrust			NE	NE
Proprioceptive positioning	2	2	2	2
Hemistand/walk	NE	NE	NE	NE
Placing–tactile	NE	NE		
Placing–visual	NE	NE		

Spinal reflexes

	Left forelimb	Right forelimb	Left hind limb	Right hind limb
Quadriceps			2	2
Extensor carpi	2	2		
Flexion	2	2	2	2
Crossed extensor	2	2	2	2
Perineal			2	2

Cranial nerves

	L	R		L	R	Comments
II, VII-Vision menace	2	2	VIII-Nystagmus, resting	2	2	
II, III-Pupils resting	2	2	VIII-Nystagmus, change	2	2	
Stim L	2	2	V-Sensation	2	2	
Stim R	2	2	VII-Facial mm	2	2	
II-Fundus	2	2	V, VII-Palpebral reflex	2	2	
III, IV, VI-Strabismus, resting	2	2	IX, X-Gag	2	2	
III, IV, VI, VIII-Strabismus, position	2	2	XII-Tongue	2	2	

Sensation (Locate and describe any abnormalities)

Hyperesthesia	0	
Superficial pain	2	
Cutaneous reflex	2	
Deep pain	NE	

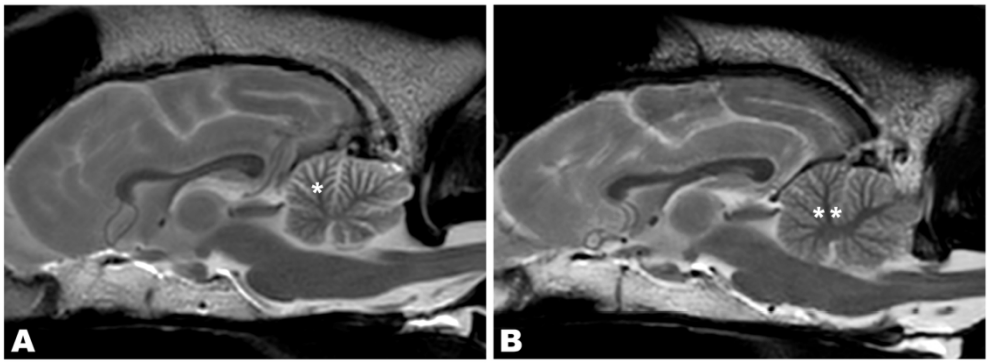

Figure 1: Sagittal T2-weighted magnetic resonance imaging (MRI) from a 4-year-old female spayed Staffordshire terrier (A) that was evaluated for progressive ataxia and episodes of collapse that localized to the cerebellum. Note the cerebellar cortical atrophy characterized by secondary widening of the cerebellar sulci with cerebrospinal fluid (CSF), outlining hypointense white matter tracts (*). These findings are consistent with cerebellar cortical degeneration of American Staffordshire terriers. Sagittal T2-weighted MRI from an age and weight matched normal Labrador Retriever (B) with idiopathic (suspected genetic) epilepsy showing normal cerebellar structure for comparison. Note the abundance of visible cerebellar cortex (**) between hypointense white matter tracts, with minimal CSF in the cerebellar sulci.

160x59mm (300 x 300 DPI)

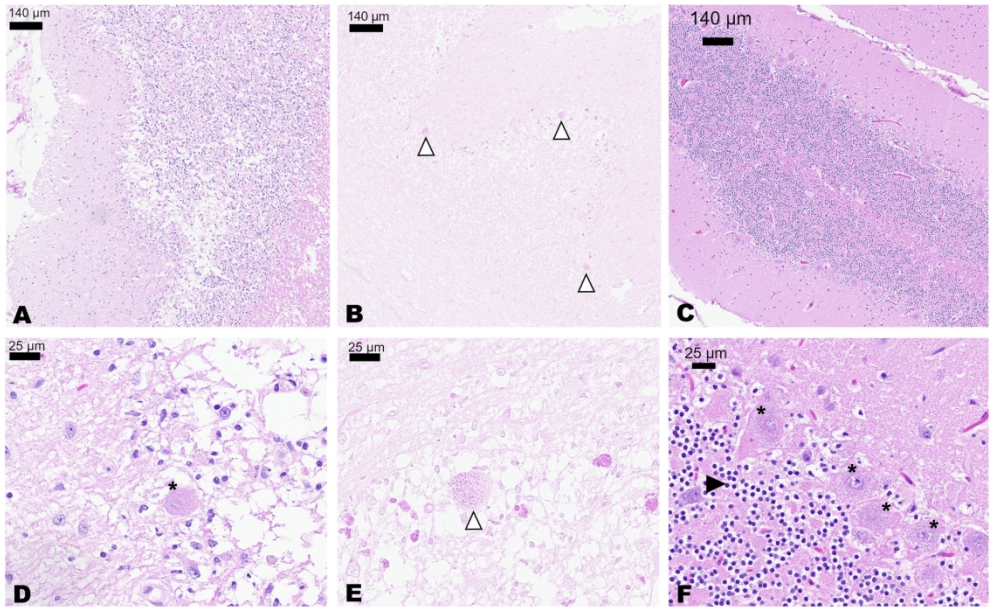

Figure 2: A-C: Low magnification photomicrographs of cerebellar folia from the affected dog (A, B) and a normal age and breed matched control (C). A, C: H&E stain, bar = 140 µm; B: Periodic Acid Schiff (PAS) stain, bar = 140 µm. Note the overall pallor in the cerebellar cortex on H&E stain and loss of Purkinje neurons in A compared to C. The few existing Purkinje neurons show PAS stain uptake (white arrowheads). High magnification photomicrographs of the cerebellar cortex from the affected dog (D, E) and the normal age and breed matched control (F). D, F: H&E stain; bar = 25 µm; E: PAS stain, bar = 25 µm. Note the vacuolation and relative lack of granule cells (black arrowhead) and Purkinje neurons (*) in D, compared to F. The remaining Purkinje neurons (white arrowhead; E), show PAS positive granules consistent with lysosomal storage products.

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