Recurrent vestibular paroxysms associated with systemic hypertension in a dog

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Case Description—A 9-year-old 19.7-kg (43.3-lb) spayed female Australian Shepherd was examined for an increase in frequency of episodic neurologic signs, often occurring upon exercise.

Clinical Findings—Between episodes of neurologic signs, the dog was considered clinically normal on the basis of findings on physical and neurologic examinations. An episode of ataxia with central vestibular signs was induced by exercising the patient in the hospital. All clinicopathologic values were within reference ranges, as were findings on magnetic resonance imaging of the brain and peripheral vestibular system. Systolic blood pressures of 180 to 200 mm Hg were recorded, and systemic hypertension was diagnosed.

Treatment and Outcome—While the dog received amlodipine and enalapril, blood pressure returned to within reference range, and episodes of neurologic signs no longer occurred. When clinical signs later recurred, systolic blood pressure was again found to be high. Following an increase in medication dosage, blood pressure normalized, and only 4 further episodes of neurologic signs were observed during a follow-up period totaling 30 months.

Clinical Relevance—Transient ischemic attack is a common diagnosis in humans but has not been described for dogs. In humans, it is defined as focal brain dysfunction caused by vascular disease that resolves completely in less than 24 hours and is often recurrent. Systemic hypertension is one of the most common preexisting conditions. We propose that the dog in the present report had clinical signs and diagnostic test results supportive of a diagnosis of transient ischemic attack. (*J Am Vet Med Assoc* 2011;239:652–655)

A 9-year-old spayed female Australian Shepherd was brought to the Tufts-Cummings School of Veterinary Medicine Emergency Service to be evaluated because of neurologic signs. The patient had no clinically relevant medical history. The owner reported a peracute onset of vomiting, ptyalism, and incoordination. The dog was a known scavenger and had been unsupervised in the woods prior to the onset of signs. Findings on physical examination were unremarkable. Neurologic examination revealed pelvic limb ataxia with frequent falling, but the dog was otherwise clinically normal. The patient was admitted and managed by withholding food and IV administration of fluids. Overnight, the patient had brief intermittent episodes of ataxia separated by periods of normal neurologic status. However, the following morning, the dog was clinically normal on the basis of findings on physical and neurologic examinations; exercising the patient failed to provoke any neurologic abnormalities.

Abdominal radiography revealed radiopaque material in the stomach, but findings were otherwise unremarkable. Results of CBC and serum biochemistry profile were within reference range limits. Urinalysis revealed a specific gravity of 1.073 without any abnormalities. Results of pre- and postprandial serum bile acids tests were within reference range limits. After 24 hours of monitoring, the patient was discharged with a tentative diagnosis of transient neurologic signs due to possible dietary indiscretion or intoxication.

Abbreviations

CVA	Cerebrovascular accident
DWI	Diffusion-weighted imaging
MRI	Magnetic resonance imaging
SBP	Systolic arterial blood pressure
TIA	Transient ischemic attack

Six weeks later, the patient was again brought to the emergency room for 2 additional neurologic episodes of similar character to the first admission. The patient had been outside unsupervised prior to each event. Findings on physical and neurologic examinations were unremarkable. The owner declined further diagnostic testing at this time.

Two days later, a further neurologic episode occurred while the dog was exercising vigorously outside with the owner. The dog was leashed at the time and had no access to toxins. The owner reported a head tilt to the left, nystagmus, and normal responsiveness. The dog gradually returned to a clinically normal state over a period of approximately 30 minutes. Upon further questioning of the owner, strenuous exercise had preceded at least 3 of the 4 episodes that she had witnessed. Normal responsiveness to auditory stimuli appeared to be present during and between episodes. At the time of hospital admission, physical and neurologic examinations were unremarkable. Following a 25-minute period of vigorous exercise, a peracute onset of vestibu-

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lar signs occurred. The patient developed generalized ataxia and began staggering to the left. A head tilt to the left was present, and the dog had wide-based positioning of the pelvic limbs. A vertical nystagmus (fast phase directed ventrally) was present. There was positional ventral strabismus in the left eye. The patient remained fully responsive throughout the episode. Findings for the remainder of a complete neurologic examination, including conscious proprioception, were unremarkable. The neurologic episode lasted about 20 minutes, steadily abating after the first 15 minutes. Nystagmus continued for as long as the head tilt and ataxia were present. Neurologic deficits indicated a lesion in the central vestibular regions of the cerebellum or brainstem. Because of lack of any apparent access, intoxication was no longer considered a differential diagnosis, and differential diagnoses included structural disease secondary to an anomalous, neoplastic, inflammatory, or vascular disorder.

Results of a CBC, serum biochemistry profile, and urinalysis were again within reference range limits. No abnormalities were detected on thoracic radiography and electrocardiography. Results of thyroid testing to measure serum free thyroxine and thyroid-stimulating hormone serum concentrations were within reference range limits. After the patient was allowed to adjust to hospitalization, SBPs of 190, 180, and 200 mm Hg were recorded by Doppler ultrasonography. Diastolic blood pressure was within the range of 70 to 120 mm Hg. These recordings were made prior to anesthesia and without the patient receiving any medications.

The dog was placed under general anesthesia for imaging and CSF collection. Magnetic resonance imaging of the head revealed that the brain and peripheral vestibular system appeared normal. T1-weighted (pre- and postcontrast), T2-weighted, fluid attenuation inversion recovery, gradient echo (T2*), and diffusion-weighted sequences were performed. Apparent diffusion coefficient maps were created from the diffusion-weighted data. Images were obtained in the transverse, sagittal, and dorsal planes (**Figure 1**). A CSF sample was obtained from the cerebellomedullary cistern; no abnormalities were detected on cytologic analysis including cell counts and protein concentration. To further investigate the systemic hypertension, abdominal ultrasonography was performed the next day, and findings were within reference range limits; adrenal gland size and shape were normal. Echocardiography revealed mild regurgitation of the mitral valve, but findings were otherwise unremarkable.

Given the lack of abnormal findings on laboratory tests and diagnostic imaging, a diagnosis of primary

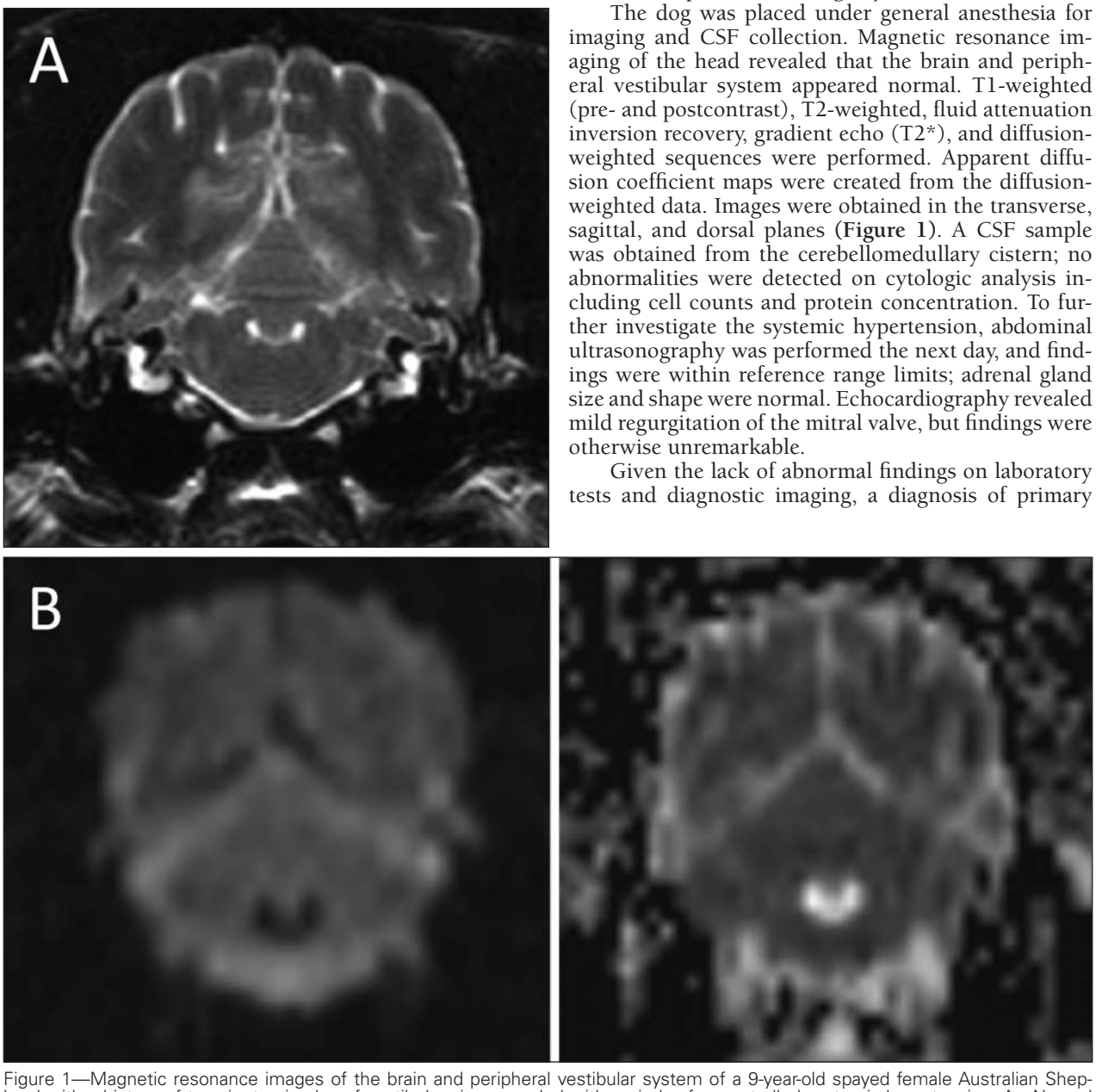

Figure 1—Magnetic resonance images of the brain and peripheral vestibular system of a 9-year-old spayed female Australian Shepherd with a history of transient episodes of vestibular signs coupled with periods of uncontrolled systemic hypertension. A—Normal T2-weighted transverse image at the level of the inner ear. B—Normal transverse diffusion-weighted image (left panel) with apparent diffusion coefficient map (right panel); level of the cerebellar medulla.

hypertension was made. Maintenance treatment with amlodipine was started at 2.5 mg (0.13 mg/kg [0.058 mg/lb], PO, q 24 h). The owner was instructed to avoid strenuously exercising the dog until the systemic hypertension was well controlled.

At follow-up 1 week later, SBP was 170 mm Hg. The amlodipine dose was increased to 2.5 mg every 12 hours. Systolic blood pressure temporarily decreased to 150 mm Hg at the 4-week recheck but subsequently increased to 170 mm Hg at 6 weeks after starting treatment. At this time, treatment with enalapril at 10 mg (0.51 mg/kg [0.23 mg/lb], PO, q 24 h) was started in addition to amlodipine administration. Three weeks later, SBP was 135 mm Hg. As no further episodes had been observed since the introduction of antihypertensive drugs, the owner was advised to return the dog to full activity under supervision only. Following reintroduction of normal exercise, no further episodes were seen initially.

One month after starting combined treatment, another neurologic episode was observed. The dog was immediately taken to a local veterinary hospital, where SBP was measured as 163 mm Hg. The enalapril dosage was increased to 10 mg every 12 hours. During the subsequent 5 months, SBP measurements were serially monitored, and most ranged from 120 to 130 mm Hg. Occasional SBP measurements over 200 mm Hg appeared to be related to excitement. Three episodes of vestibular signs occurred during this 5-month period. After a further 3 months, there was a single episode of vestibular signs. As of 19 months since this final event, the owner had reported no further neurologic problems (total follow-up time of 30 months). The patient had remained on the same regimen of amlodipine (2.5 mg, q 12 h) and enalapril (10 mg, q 12 h), and monthly SBP measurements continued to range from 120 to 130 mm Hg.

Discussion

Transient ischemic attacks are common in the human population, with 50,000/y occurring in the United States alone.[1] They are defined as temporary, focal brain (or retinal) deficits secondary to vascular disease that resolve completely in less than 24 hours.[1] Deficits lasting more than 24 hours are known as CVAs or strokes, whereas TIAs are commonly referred to as ministrokes.[1,2] Transient ischemic attacks represent a brief period of inadequate perfusion in a territory of the carotid or vertebrobasilar arteries, whereas CVAs are caused by persistent occlusion of flow. The 24-hour limit is arbitrary, and TIAs lasting this long in humans are rare. Most attacks last < 30 minutes, and the median duration of clinical signs in the vertebrobasilar distribution is only 8 minutes.[3] Other causes of transient neurologic deficits in humans include partial seizure and subdural hematoma.[1] Paroxysmal peripheral vestibular episodes may be seen with benign paroxysmal positioning vertigo (thought to be due to formation of otoliths in the semicircular canals) and Meniere's disease (rupture of the endolymphatic membrane).[4]

Typical causes of TIAs in humans are thrombi or vasospasm related to systemic hypertension, atherosclerosis, or diabetes mellitus. Systemic hypertension concurrently affects 63% of patients.[5] Long-standing systemic hypertension causes atherosclerosis, and this in turn may lead to thrombosis, vasospasm, or both.[1,3] Emboli secondary to cardiovascular disease (eg, valvular disease) are also considered an important cause of TIAs in humans. Occasional causes of TIAs include emboli from other sources (bacteria, tumor, or air), hyperviscosity, vasculitis, or trauma to the vasculature of the head and neck.

Clinical signs of a TIA are well recognized as a major warning that a full CVA may later occur. Transient ischemic attack is the greatest risk factor for CVA (odds ratio, 5.6), compared with all other implicated factors, such as atrial fibrillation, hypertension, diabetes mellitus, congestive heart failure, or smoking (odds ratios, 2.0 to 2.1 for each factor).[6] Within 90 days of a TIA, 25% of humans will have a CVA or another adverse event, such as a second TIA or death.[7] In total, a third of humans that have a TIA will go on to have a CVA.[1]

Diffusion-weighted imaging is an advanced MRI technique that has revolutionized the early detection of CVAs in humans. Decreased Brownian motion of intracellular water molecules (decreased diffusion) produces a hyperintense area on DWI. Apparent diffusion coefficient mapping of the DWI signal reveals a hypointense signal in regions of decreased perfusion. Decreased diffusion of intracellular water molecules occurs immediately following ischemia and is thought to be associated with alterations of the ratio between intra- and extracellular volumes, of the permeability of cell membranes to water, and of tissue microstructures (eg, macromolecules and intracellular organelles). As a result, DWI can detect CVA within as little as 11 minutes, whereas a CVA will not be evident by use of conventional MRI for up to 12 to 14 hours.[8,9] As such, DWI is a more sensitive imaging technique in the diagnosis of acute CVA.[8,10]

Normal findings on DWI and conventional MRI scans are more consistent with TIA than CVA, although the prevalence of positive findings is increasing as technology advances. In the first reports of DWI in the detection of TIA, no abnormal findings were identified in patients with attacks lasting < 5 minutes. Diffusion-weighted imaging abnormalities were present in about two-thirds of cases in which clinical signs lasted 12 to 24 hours.[11,12] In a later study,[10] abnormalities were found in only 14.0% of humans with TIA, compared with 56.9% of humans with CVA. Findings of a recent study[8] demonstrated a 33% likelihood of finding abnormalities on DWI for TIA of 5 to 30 minutes' duration, compared with a > 95% likelihood of finding abnormalities on DWI for CVA. In patients with TIA that do have abnormalities detected on DWI, such changes may still be present after resolution of the clinical signs.[10–12] Transient ischemic attack typically leaves no lasting morphological damage, and consequently, conventional MRI findings are normal.

Although TIAs are common in human patients, they are rarely recognized in dogs. No clinical reports of TIA in dogs exist to the authors' knowledge. However, in reports[13,14] describing CVA in dogs, a total of 6 dogs were reported to have had prior < 10-minute episodes of self-resolving neurologic abnormalities. In each case, the re-

current episodes were vestibular in nature and preceded a CVA affecting the rostral cerebellar artery territory. The authors speculated that these preceding episodes represented TIAs. Prior episodes of temporary vestibular signs were also been reported in 1 dog with a middle cerebral artery CVA as detected on MRI and histologic evaluation.[15]

We suggest that TIAs in the central vestibular regions of the cerebellum or brainstem were responsible for the vestibular episodes in the dog of this report. A partial seizure was considered unlikely as the cause of paroxysmal vestibular signs. There was normal mentation throughout the episodes, the episodes usually occurred in association with exercise, and there was no postictal phase. Events ultimately abated after the antihypertensive medication regime was optimized, and antiepileptic drug treatment was never used. The transient nature of the signs and normal findings on diagnostic tests and imaging aided in excluding anomalous, metabolic, neoplastic, nutritional, inflammatory, and traumatic disease processes of the central vestibular system. The asymmetric neurologic deficits aided in excluding degenerative, metabolic, nutritional, and toxic disorders. Idiopathic vestibular disease frequently occurs in dogs but is associated with peripheral vestibular signs and not vertical nystagmus, gradually resolves over ≥ 1 to 2 weeks, rarely affects the same dog more than once, and typically occurs in patients older than 9 years (the median age being 12.5 years).[16–19]

A vascular etiology was therefore suspected in the dog of this report. The occurrence of the episodes upon exercise and during periods of uncontrolled hypertension supports this conclusion. Furthermore, the territory most commonly affected in ischemic CVA of dogs is that of the rostral cerebellar artery, and the resulting neurologic deficits are similar to the transient signs shown by the dog in the present report.[13,14,20] Systemic hypertension (29% of cases) is associated with CVA in dogs; other comorbid conditions identified included chronic kidney disease (24%), untreated hyperadrenocortism (18%), and single cases of aortic stenosis, diabetes mellitus, and pheochromocytoma.[21] Given the association of hypertension with CVA in dogs as well as with TIA and CVA in humans, further investigations are needed to assess whether such an association exists between hypertension and TIA in dogs. In the treatment of systemic hypertension in dogs, treatment should be escalated whenever SBP is ≥ 150 mm Hg and there is evidence of ocular or CNS target organ damage,[22] and we used this premise to manage the blood pressure of this individual patient. This is comparable to the guidelines for TIA in humans, for whom SBP should be maintained at < 140 mm Hg, or < 160 mm Hg for the elderly.[1]

In conclusion, we believe that the dog in the present report had clinical signs and diagnostic test results supportive of TIA. Transient episodes of vestibular signs were peracute, stereotypical in nature, and followed by a rapid and complete return to normal neurologic status. These episodes were temporally related with periods of uncontrolled systemic hypertension and with exercise. Periods of normotension were associated with infrequent or no vestibular episodes. Conventional MRI and DWI studies[13,14,20,21,23] failed to reveal imaging abnormalities that typify CVA in dogs. As a CVA has not occurred in this patient to date, it is unclear whether these episodes are predictive indicators of an eventual CVA in this individual patient. Additional studies of suspected cases with more sophisticated imaging methods and long-term follow-up may lead to a heightened awareness and recognition of TIAs and their possible association with CVA in dogs.

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