

## Case Report

*J Vet Intern Med* 2016**Convergence-Retraction Nystagmus Associated with Dorsal Midbrain Lesions in Three Dogs**

A.H. Crawford, E. Beltran, R. Lam, and P.J. Kenny

Convergence-retraction nystagmus is an irregular, jerky nystagmus in which both eyeballs rhythmically converge and retract into the orbit, particularly on attempting an upward gaze.<sup>1</sup> In humans it is seen as part of Parinaud's syndrome, also known as dorsal midbrain syndrome, in which a lesion of dorsally located midbrain structures (the ventral pretectum, the periaqueductal area, and the medial longitudinal fasciculus in the dorsal tegmentum) prevents upward or downward movement of the eyes.<sup>2-4</sup> It has been hypothesized that convergence-retraction nystagmus is caused by damage (ischemia, neoplasia, compression, or demyelination) to supranuclear fibers that have an inhibitory effect on the convergence neurons or divergence neurons in the midbrain, resulting in a sustained discharge of medial rectus and other extraocular muscle neurons.<sup>2,3</sup> The rostral interstitial nuclei of the medial longitudinal fasciculus (RINMLF) of the midbrain, located dorsal to the oculomotor nuclei, contain the final relays producing all vertical saccades, and hence it has been suggested that Parinaud's syndrome may result from damage to their neuronal cell bodies, as well as their afferent and efferent pathways.<sup>2,4</sup>

Convergence-retraction nystagmus is a highly localizing clinical sign that to the best of our knowledge has not yet been described in the dog. Here, we report 3 large breed dogs that were presented with convergence-retraction nystagmus and in which magnetic resonance imaging (MRI) identified focal lesions within the dorsal midbrain.

Case 1: An 11-year, 5-month-old male neutered Staffordshire Bull Terrier was presented with a 14-day history of acute onset, nonprogressive vestibular ataxia with lethargy and disorientation. General physical examination was normal. On neurological examination,

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**Abbreviations:**

ALKP	alkaline phosphatase
ALT	alanine transferase
FFE	fast field echo
FLAIR	fluid-attenuated inversion recovery
MRI	magnetic resonance imaging
RINMLF	rostral interstitial nuclei of the medial longitudinal fasciculus
RI	reference interval
T1W	T1 weighted
T2W	T2 weighted
TE	echo time
TR	repetition time
TSH	thyroid-stimulating hormone

the dog was found to be mildly obtunded with a mild right-sided head tilt and circling to the right. Convergence-retraction nystagmus was noted (Video S1), with decreased vestibulo-ocular reflex bilaterally. The remainder of the neurological examination was normal and the findings were considered consistent with a right brainstem neurolocalization.

The CBC results were within reference intervals (RIs). Serum biochemistry results included a mildly increased alkaline phosphatase (ALKP) activity (313 U/L; RI, 19–285 U/L), alanine transferase (ALT) activity (171 U/L; RI, 13–88 U/L), and calcium concentration (2.73 mmol/L; RI, 2.13–2.7 mmol/L). Serum thyroxine and thyroid-stimulating hormone (TSH) concentrations were within normal limits. Prothrombin time and activated partial thromboplastin time were within normal limits. Noninvasive blood pressure assessment identified a pressure of 170–175 mmHg. Urine-specific gravity was 1.043, and urine chemistry dipstrip analysis and sediment examination were normal. A Baermann test for *Angiostrongylus* was negative.

The dog underwent general anesthesia. A combination of acepromazine maleate (0.01 mg/kg IV) and methadone (0.1–0.2 mg/kg IV) was used for premedication, followed by induction with propofol (4–6 mg/kg IV) and maintenance of anesthesia with isoflurane in oxygen.

A MRI examination was performed<sup>a</sup> and included T2-weighted (T2W) (repetition time, [TR] [ms], echo time [TE], [ms] 3333/110) sagittal and transverse images, T2W fluid attenuated inversion recovery (FLAIR) (TR/TE, 3612/80, inversion time [TI] [ms] 2000) transverse images, and T2\*W fast field echo (FFE) transverse images. Sagittal and transverse, T1-weighted (T1W) (TR/TE, 515/15) images were acquired before and after IV administration of gadolinium contrast (0.1 mmol/kg, gadobutrol<sup>b</sup>). Slice

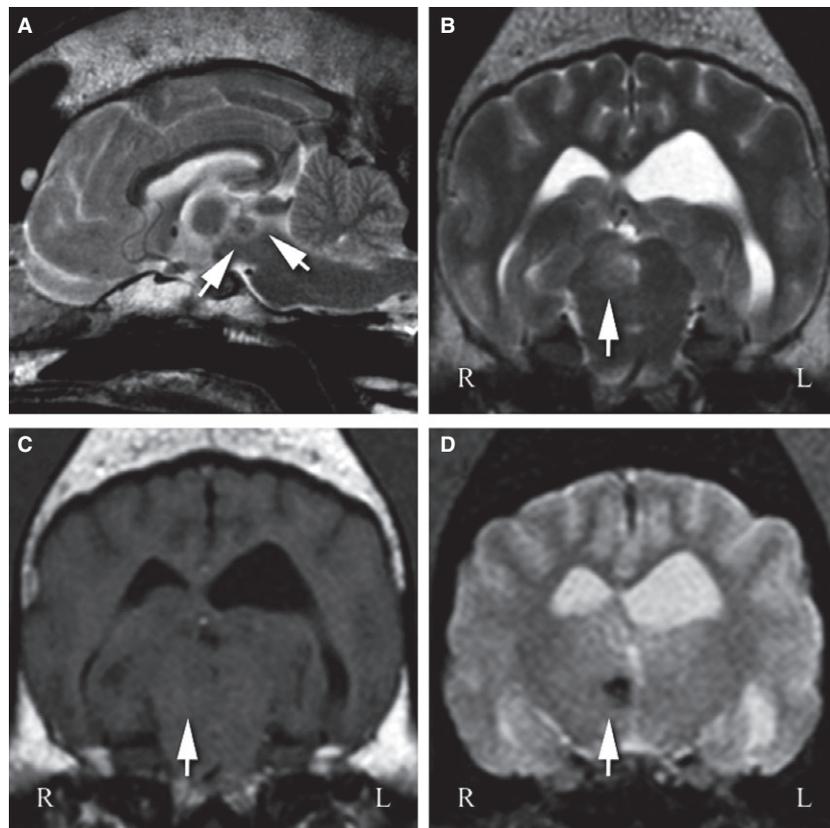
thickness was 1.75 mm in the sagittal and 2 mm in the transverse planes with an interslice gap of 0.9 mm in all planes. A rounded, 5 mm diameter, poorly demarcated lesion was identified within the right dorsal midbrain, adjacent to the midline and extending rostrally to the caudal margin of the interthalamic adhesion (Fig 1). The lesion was iso- to hypointense-to-normal-gray-matter on T1W images, hyperintense on T2W and FLAIR sequences, with a central signal void on FFE sequences. The lesion did not show enhancement after gadolinium contrast administration, and there was evidence of a mild mass effect. These findings were most consistent with a cerebrovascular accident, potentially with a central hemorrhagic component given the signal void on FFE sequences, with other differential diagnoses including inflammatory and neoplastic disease. Computed tomography was performed with a 16-slice scanner<sup>c</sup> to evaluate for evidence of a predisposing cause for cerebrovascular disease. This examination of the head, thorax, and abdomen identified mild bilateral rhinitis and several small, round nodules within the spleen. Analysis of cerebrospinal fluid was not performed.

The dog was discharged from the hospital 36 hours after admission and made a full recovery within 12 days, with no recurrence of the neurological deficits. This patient was euthanized 34 months later because of severe degenerative joint disease and weight loss.

Case 2: A 10-year, 8-month-old male neutered Rotweiler was presented for sudden onset abnormal mentation with vacant episodes. The dog had been diagnosed with diabetes mellitus 8 months previously, and was well controlled with 54 IU of porcine lente insulin administered SC q12h.

General physical examination identified bilateral elbow crepitus with decreased range of flexion, but was otherwise unremarkable. On neurological examination, the dog was found to be quiet, but alert and responsive. The head was held elevated with dorsal extension of the neck and very mild right-sided head tilt. The sclera of both eyes could be seen above the iris, with the distance between the superior eyelid and iris being increased with an upward gaze (Fig 2). Intermittent convergence-retraction nystagmus was noted, and was found to be most apparent when the head was held elevated (Video S2). The remainder of the neurological examination was unremarkable, and a neurolocalization of right brainstem was determined.

The CBC was within RIs. Serum biochemistry results included increased serum potassium concentration (5.8 mEq/L; RI, 3.9–5.5 mEq/L), inorganic phosphorus concentration (2.62 mmol/L; RI, 0.8–2 mmol/L), urea concentration (12.6 mmol/L; RI, 3–9.1 mmol/L), creatinine concentration (146  $\mu$ mol/L; RI, 59–138  $\mu$ mol/L), cholesterol concentration (16.8 mmol/L; RI,



**Fig 1.** Case 1 T2-weighted sagittal image of the brain (A) and T2W (B), T1W (C) transverse images at the level of the rostral midbrain revealed a round lesion adjacent to the midline. The lesion (indicated by the arrows) is hyperintense-to-normal gray matter on T2W sequences, iso- to hypointense on T1W sequences. FFE image at the level of the thalamus (D) shows a signal void in the rostral aspect of the lesion.



**Fig 2.** Case 2 demonstrated elevation of the head with extension of the neck and very mild right-sided head tilt. The sclera of both eyes could be seen dorsal to the iris, with the distance between the superior eyelid and iris being further increased with an upward gaze.

3.3–8.9 mmol/L), and creatine kinase activity (421 U/L; RI, 61–394 U/L), with a mildly decreased serum albumin concentration (26.6 g/L; RI, 28–39 g/L). All other variables were within normal limits. Serum thyroxine and TSH concentrations were within normal limits. Noninvasive blood pressure assessment identified a mean pressure of 170 mmHg. Urine-specific gravity was 1.012, urine chemistry dipstrip analysis identified 2+ blood, but was otherwise unremarkable, as was sediment examination. Urine bacteriological culture was negative.

The dog underwent general anesthesia and MRI of the brain as described above and a small, focal, right-sided, well-demarcated T2W, FFE and FLAIR hyperintense-to-normal-gray matter lesion was indentified within the right dorsal midbrain (Fig 3). The lesion was approximately 2 mm in diameter, adjacent the midline (right sided) and ventrolateral to the mesencephalic aqueduct. No contrast enhancement was detected, nor was there evidence of mass effect. These imaging findings were consistent with a cerebrovascular accident, with other differential diagnoses including inflammatory and neoplastic disease.

Analysis of a cerebrospinal fluid sample obtained from the cisterna cerebellomedullaris had a total nucleated cell count of 1/ $\mu$ L (RI, 0–5/ $\mu$ L), red blood cell count of 3/ $\mu$ L, and a total protein concentration of 0.28 g/L (RI, 0–0.25 g/L). Cytological evaluation disclosed low cellularity, consisting primarily of monocytes. Thoracic and abdominal CT detected mild elbow osteoarthritis and degenerative intervertebral disk disease, but was otherwise unremarkable.

The dog showed steady improvement in mentation and demeanor over the subsequent 48 hours, at which time it was discharged from the hospital. On telephone discussion with the owner 6 months after hospital discharge, the dog was reported to have made a full recovery with no apparent residual neurological deficits.

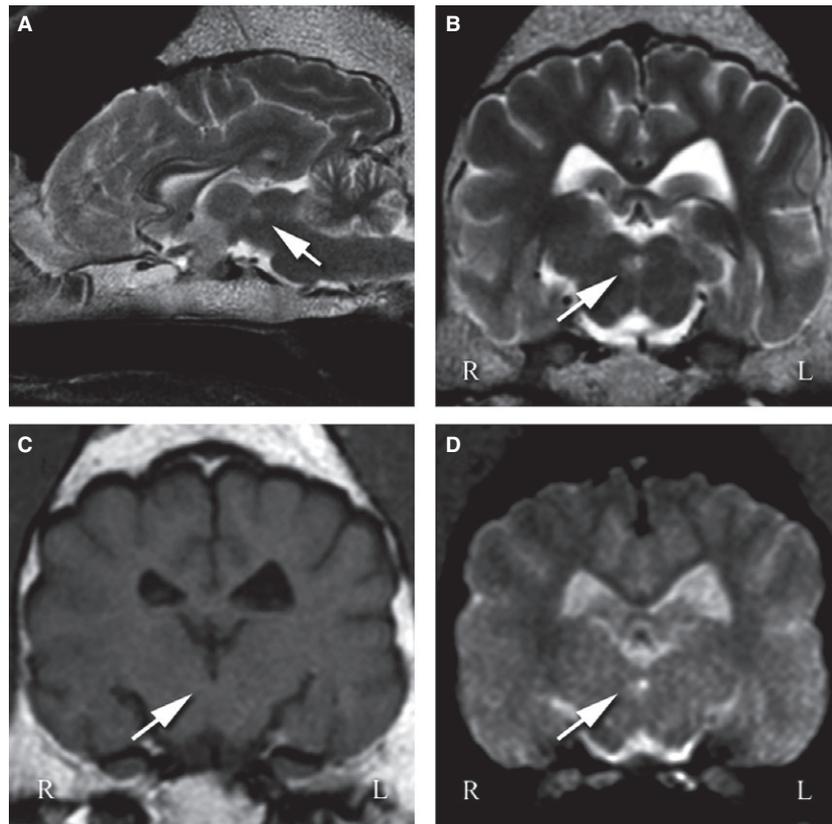
Case 3: A 7-year, 6-month-old male neutered English Bull Terrier was presented for further investigation of a 24-hour history of acute onset, right-sided head tilt. Physical examination findings were unremarkable. Neurological examination identified a mild right-sided head tilt, decreased menace response in both eyes with normal vision and convergence-retraction nystagmus (Video S3). The remainder of the neurological examination was normal, and a neurolocalization of right brainstem was determined.

A CBC disclosed a mild increase in the packed cell volume (59%; RI, 37–55%) and hemoglobin (20.1 g/dL; RI, 12–18 g/dL). Serum biochemistry results included a mild decrease in sodium concentration (137 mEq/L; RI, 142–153 mEq/L) and a mild increase in ALT activity (106 U/L; RI, 13–88 U/L). Serum thyroxine and TSH concentrations were within normal limits.

The dog underwent general anesthesia and MRI of the brain as described above, which identified a small, focal, left-sided, well-demarcated T2W, FFE, and FLAIR hyperintense-to-normal-gray matter lesion within the dorsal and rostral midbrain (Fig 4). The lesion was approximately 3 mm in diameter, adjacent to the midline (left-sided), and ventrolateral to the mesencephalic aqueduct. No contrast enhancement was detected, nor was there evidence of mass effect. These imaging findings were consistent with a cerebrovascular accident, but other differential diagnoses included inflammatory and neoplastic disease. Computed tomography of the thorax and abdomen identified a mild lumbosacral intervertebral disk protrusion and a very mild jejunal lymphadenopathy, but was otherwise unremarkable. Cerebrospinal fluid collection was attempted from the cerebellomedullary cistern, but was unsuccessful.

The dog made an uneventful recovery and on telephone discussion with the owner 10 months after hospital discharge, the dog was reported to have made a full recovery with no apparent residual neurological deficits.

Physiological nystagmus (the vestibulo-ocular reflex) is an involuntary, rhythmic ocular movement, the purpose of which is to keep the retina fixed on a visual target as the head rotates.<sup>5,6</sup> Head rotation stimulates hair cell receptors in the cristae ampullares of the semicircular canals of the inner ear. This afferent input is transmitted via cranial nerve VIII (vestibulocochlear nerve) to the vestibular nuclei in the medulla oblongata, and then through the medial longitudinal fasciculus to the brainstem nuclei of cranial nerves III (oculomotor nerve), IV (trochlear nerve), and VI (abducent nerve) to elicit movement of the eyeball.<sup>7</sup> Physiological nystagmus occurs in response to head rotation, with the rapid phase of eyeball movement in the direction of rotation. Pathological nystagmus occurs spontaneously (spontaneous nystagmus) or when an abnormal head posture is induced (positional nystagmus) as a result of vestibular



**Fig 3.** Case 2 T2-weighted sagittal image of the brain (A) and T2W (B), T1W (C), and FFE (D) transverse images at the level of the rostral midbrain revealed a small round lesion adjacent to the midline (right sided) and ventrolateral to the rostral part of the mesencephalic aqueduct. The lesion (indicated by the arrows) is hyperintense-to-normal-gray matter on T2W and FFE sequences, and is iso- to hypointense on T1W sequences.

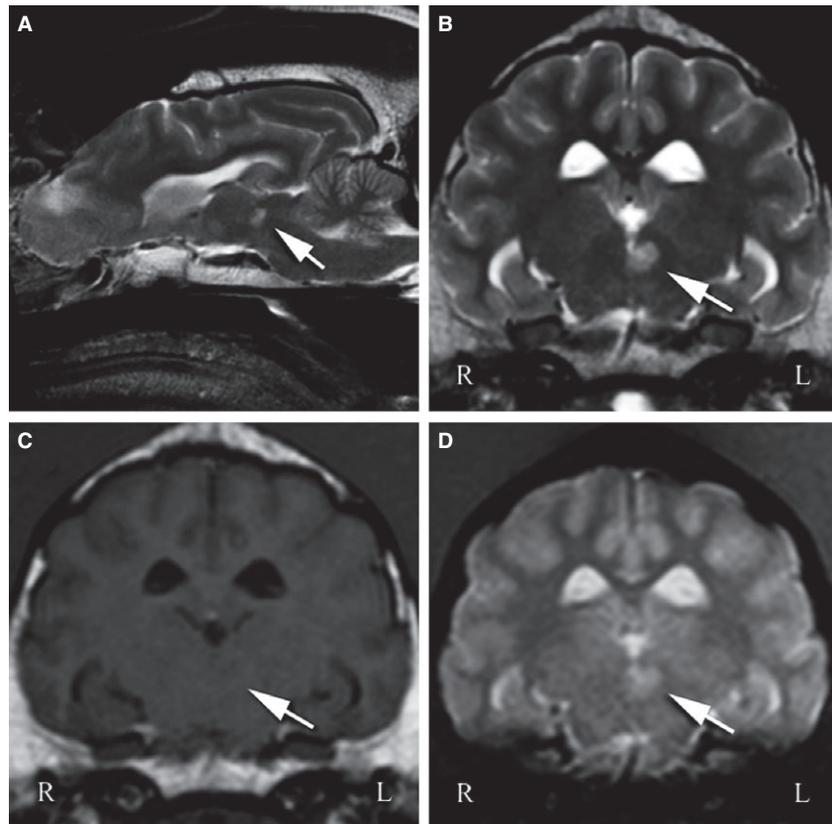
system dysfunction.<sup>5,6</sup> Pathological nystagmus is categorized as horizontal, vertical, or rotary depending on the direction of eyeball movement. Furthermore, it can be described as conjugate, when the eyeballs are each moving in the same direction, or dysconjugate, in which each eyeball is moving in a different direction.<sup>8</sup>

In this report, we describe 3 dogs that were presented with convergence-retraction nystagmus; an irregular, jerky movement of the eyeballs, which rhythmically converge and retract into the orbit, particularly on attempting an upward gaze.<sup>1</sup> This nystagmus differs from horizontal, vertical, or rotary nystagmus, in which an oscillation is seen with both eyes moving in the same direction and with no eyeball retraction. It results from simultaneous contraction of all of the extraocular muscles in response to efforts to change the direction of gaze. This rhythmic contraction is thought to result from a sustained discharge of axons in the medial longitudinal fasciculus.<sup>2,3</sup> The RINMLF of the midbrain (Fig 5), located dorsal to the oculomotor nuclei, contain the final relays producing all vertical eye movements and hence compromise of the neuronal cell bodies, their afferent and efferent pathways or both are thought to generate convergence and retraction of the eyeballs.<sup>4</sup> Given the lack of apparent direct vestibular system involvement, it can be debated as to whether or not

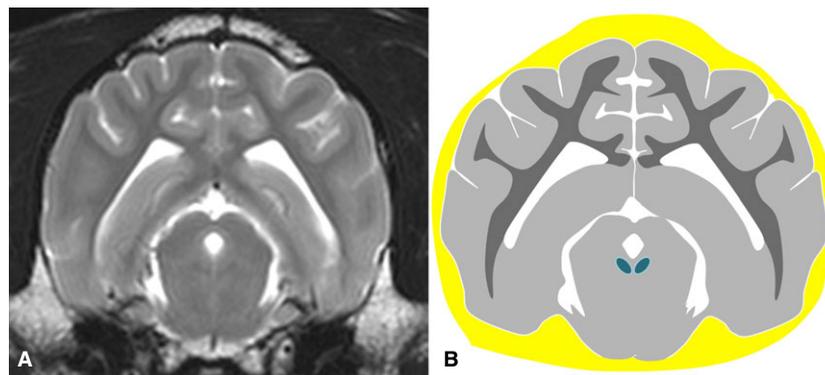
these convergent and retraction movements should be referred to as a nystagmus.

In humans, convergence-retraction nystagmus typically is accompanied by upward or downward gaze paralysis or both, paresis of the pupils, and eyelid retraction.<sup>2,4</sup> Lesions affecting the dorsal midbrain can lead to functional disruption of the rostral or caudal colliculi or both, oculomotor nuclei and Edinger-Westphal nuclei (parasympathetic oculomotor), causing motor dysfunction of the eye. The dog in case 2 presented with an abnormal posture, typically sitting with the head markedly elevated and the neck extended (Fig 2). This posture was presumed to represent active compensation for inability to elevate the gaze. In addition, the distance between the superior eyelid and iris would increase on attempts to gaze upward. In humans this finding is called “Collier’s sign”, and results from a combination of eyelid retraction and vertical gaze palsy caused by dorsal midbrain lesions. Detailed neuro-ophthalmic examination therefore is recommended in any patient presenting with convergence-retraction nystagmus to identify subtle deficits of ocular movement.

All dogs had signs of vestibular dysfunction, albeit mild, on presentation. Thalamic lesions are known to generate signs of vestibular dysfunction (e.g., head tilt,



**Fig 4.** Case 3 T2-weighted sagittal image of the brain (A) and T2W (B), T1W (C), and FFE (D) transverse images at the level of the rostral midbrain revealed a round, well-demarcated lesion adjacent to the midline (left sided) and ventrolateral to the rostral part of the mesencephalic aqueduct. The lesion (indicated by the arrows) is hyperintense-to-normal-gray matter on T2W and FFE sequences, and is iso- to hypointense on T1W sequences.



**Fig 5.** T2-weighted transverse image of the brain at the level of the rostral midbrain (A) and schematic depiction (B) to show the location of the rostral interstitial nuclei of the medial longitudinal fasciculus (RINMLF), highlighted as green ovals.

tendency to circle) in dogs.<sup>9</sup> All dogs described here presented with a right-sided head tilt: in dogs 1 and 2 the head tilt was ipsilateral to the lesion, and in dog 3 it was contralateral. Head tilts associated with ventrolateral thalamic infarcts are reported to be ipsilateral, and head tilts associated with paramedian infarcts are contralateral to the side of the lesion.<sup>9</sup> Presumably, the lesions in dogs 1 and 2 reported here interrupted the pathway between the right ventrolateral thalamus and

midbrain, whereas the lesion in dog 3 interrupted the pathway between the left paramedian thalamus and midbrain. The mediodorsal nucleus of the thalamus, affected in paramedian infarcts, has direct connections with the cerebellum<sup>10</sup> and several brainstem structures including the interstitial nucleus of Cajal.<sup>9,11</sup> The medial longitudinal fasciculus also lies in close proximity to vestibulo-thalamic pathways, which when lesioned induce vestibulo-perceptive dysfunction.<sup>12</sup>

The imaging characteristics of the lesions in the 3 cases reported here were consistent with a cerebrovascular accident.<sup>9,13</sup> However, only a tentative diagnosis can be made in the absence of histopathological confirmation. The term “cerebrovascular accident” is defined as any abnormality of the brain resulting from a pathological compromise of its blood supply. Such pathological compromise may be the result of a thrombus or embolus occluding the blood vessel lumen, rupture of the blood vessel wall, altered blood vessel wall permeability, or altered viscosity of the blood.<sup>14</sup> These events may represent idiopathic vasculopathies, or may arise secondary to inflammatory, infectious, systemic, or neoplastic disease. In humans, dorsal midbrain syndrome has been reported as a consequence of numerous diseases in addition to cerebrovascular accidents, including pineal gland neoplasia, angiomas, multiple sclerosis, acute hydrocephalus, generalized seizures, and infectious disease (eg, toxoplasmosis).<sup>2</sup> Similar conditions also should be considered as differential diagnoses in dogs presented with convergence-retraction nystagmus.

Convergence-retraction nystagmus appears to be a highly specific neurological sign localizing to the dorsal midbrain (tectum and dorsal aspect of the tegmentum). The presence of convergence-retraction nystagmus would help discriminate between central and peripheral lesions in animals presented with vestibular dysfunction. If it is the predominant neurological sign, as in the dogs described here, convergence-retraction nystagmus likely suggests a focal lesion, which in combination with patient signalment and history, may be more suggestive of certain etiologies (e.g., vascular, inflammatory, neoplastic) than others. A clearly defined problem and list of differential diagnoses allows for a rational and targeted diagnostic plan. Convergence-retraction nystagmus therefore should be added to the categories of nystagmus described in the dog, and recognized as a consequence of a central nervous system lesion, specifically of the dorsal midbrain.

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### Footnotes

<sup>a</sup> Intera 1.5T, Philips Medical Systems, Best, the Netherlands

<sup>b</sup> Gadovist, Bayer, Bayer House, Strawberry Hill, UK

<sup>c</sup> Philips Mx8000 IDT, Philips

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*Conflict of Interest Declaration:* Authors declare no conflict of interest.

*Off-label Antimicrobial Declaration:* Authors declare no off-label use of antimicrobials.

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### Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

**Video S1.** Convergence-retraction nystagmus in case 1.

**Video S2.** Convergence-retraction nystagmus in case 2.

**Video S3.** Convergence-retraction nystagmus in case 3.