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CASE REPORT OPEN ACCESS

Dogs

Convergence Retraction Nystagmus Secondary to Central Nervous System Disseminated *Coccidioides Immitis* Infection in a Dog

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ABSTRACT

This report describes a Belgian Malinois dog residing in metropolitan Phoenix, Arizona that was presented to a veterinary neurology center with abnormal eye movements as his only clinical sign. On examination, clinical signs were isolated to convergence-retraction nystagmus. A brain MRI was performed which identified two well-demarcated, T2-hypointense and T1-isointense, avidly contrast enhancing mass lesions with moderate to severe perilesional T2 and FLAIR hyperintensity within the left frontal lobe and left dorsal midbrain. Imaging characteristics were most consistent with *Coccidioides immitis* fungal granulomas and serology was supportive of Coccidioidomycosis infection. The patient's clinical signs resolved quickly with antifungal and anti-inflammatory therapies, and brain granulomas were resolved or resolving on repeat imaging 10 months after initial diagnosis. To the authors' knowledge, this is the first report of convergence-retraction nystagmus secondary to an infectious etiology described in a canine patient.

1 | Signalment, History and Clinical Findings

A 7-year and 5-month-old castrated male Belgian Malinois dog residing in Arizona was presented to a referral veterinary neurological center with abnormal eye movements of 72-h duration. Initial evaluation occurred within 24-h with the primary care veterinarian and consisted of physical examination, CBC, chemistry, total T4 and serology for *Ehrlichia canis* antibody by IFA and *Coccidioides immitis* immunodiffusion titer through a commercial laboratory (Idexx laboratories). Prior to referral for neurological examination, all blood test results were unremarkable with *C. immitis* results pending. Intraocular pressures were measured in both eyes and were normal (15 mmHg OD, 13 mmHg OS) and three-view thoracic radiographs were also unremarkable. Prior to these abnormal eye movements, the patient had no pertinent medical history.

On neurological examination, the patient was bright, alert, and appropriately responsive to auditory, tactile and visual cues. He was ambulatory without overt paresis or ataxia. He had normal facial symmetry, palpebral reflex and menace responses in both eyes. The globes spontaneously, symmetrically, rhythmically pulsated and retracted into the orbit with convergent trajectory, and these movements were amplified in frequency with an

Abbreviations: AGID, agar gel immunodiffusion; ALP, alkaline phosphatase; ALT, alanine transaminase; CBC, complete blood count; CSF, cerebrospinal fluid; IFA, immunofluorescence antibody; IFA, immunofluorescence antibody; MRI, magnetic resonance imaging; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; T4, thyroxine; VF, Valley Fever.

upward gaze. An oculocephalic reflex was present bilaterally, but normal physiologic eye movements were replaced by convergent and retracted globe movements. During upward gaze, the superior eyelids elevated dorsally, and nictitating membranes elevated. Based on clinical history and published reports in patients with these specific eye movements, termed convergence-retraction nystagmus, the patient neuroanatomically localized to a lesion within the dorsal midbrain. Differential diagnoses included vascular accident as a strong concern based on published reports, with infectious, non-infectious inflammatory and neoplastic etiologies also considered.

2 | Imaging, Diagnosis and Outcome

The patient was premedicated with butorphanol 0.1 mg/kg intravenously, anesthesia induced with propofol titrated to effect (4–6 mg/kg intravenously) and anesthesia maintained with isoflurane gas. The patient was positioned in dorsal recumbency for head MRI using a 16-channel extremity knee coil (1.5T HD T/R Knee Array, Invivo Corporation, Gainesville, FL). 2D images were obtained with a 1.5T magnet (Signa HDxt 1.5 T, General Electric Healthcare, Chicago, IL) with the following pulse sequences obtained: T2-weighted images in the transverse and sagittal planes; T2-weighted gradient resonance echo (T2*), fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted images in transverse plane; pre-contrast T1-weighted image in transverse plane, and post-contrast T1-weighted images in transverse, sagittal and dorsal planes. The imaging acquisition parameters were as follows: T2-weighted spin-echo (SE) sequences, repetition time (TR) = 3167–3800 ms and echo time (TE) = 97–99 ms; FLAIR (TR 8602 ms, TE 148 ms, inversion time 2150 ms); T2* (TR 425 ms, TE 8 ms); diffusion weighted imaging (echo planar) (TR 8000 ms, TE 92 ms); pre- and post-contrast T1-weighted sequences (TR 516–667 ms, TE 10–11 ms). Slice thickness ranged from 3 to 5 mm. Gadobenate dimeglumine 529 mg/mL (Multihance, Bracco Diagnostics, Monroe Twp, NJ) was the paramagnetic contrast agent used intravenously at a dose of 0.2 mL/kg (7.1 mL).

Two T1-isointense, avidly and homogenously contrast-enhancing, T2-hypointense, intra-axial mass lesions were noted within the left ventral frontal lobe and the left dorsal midbrain, respectively. Lesions were associated with moderate, poorly defined, non-enhancing, T2 and FLAIR perilesional hyperintensity, more significantly surrounding the midbrain lesion than the frontal lobe lesion (Figure 1a,b). Neither susceptibility artifact nor restricted diffusion was associated with these lesions. The left midbrain lesion was estimated at 4.8 mm (H) × 3.4 mm (W) × 4.3 mm (L) (Figures 2 and 3) and the left frontal lobe lesion was estimated at 2.1 mm (H) × 2.1 mm (W) × 6.0 cm (L) (Figure 4). The remainder of the brain including the ventricular system imaged normally. The primary differential diagnosis was multifocal, intra-axial *C. immitis* fungal granulomas. The images were reviewed by a second-year veterinary neurology resident, a board-certified veterinary neurologist, and a board-certified veterinary radiologist, all of whom were in agreement with lesion location and description.

Collection of cerebrospinal fluid from the cisterna magna was performed using 1.5″ spinal needle. The patient was placed in lateral recumbency and fur overlying the atlantooccipital joint shaved and skin aseptically prepared. 1.5 mL of clear spinal fluid was collected by direct flow into a single-use plastic microcentrifuge tube. Cerebrospinal fluid (CSF) analysis was performed and analysed in-house. A hemocytometer was prepared using a sample of CSF diluted 1:1 with filtered new methylene blue stain (Jorgensen Laboratories; Loveland, CO) within one chamber,

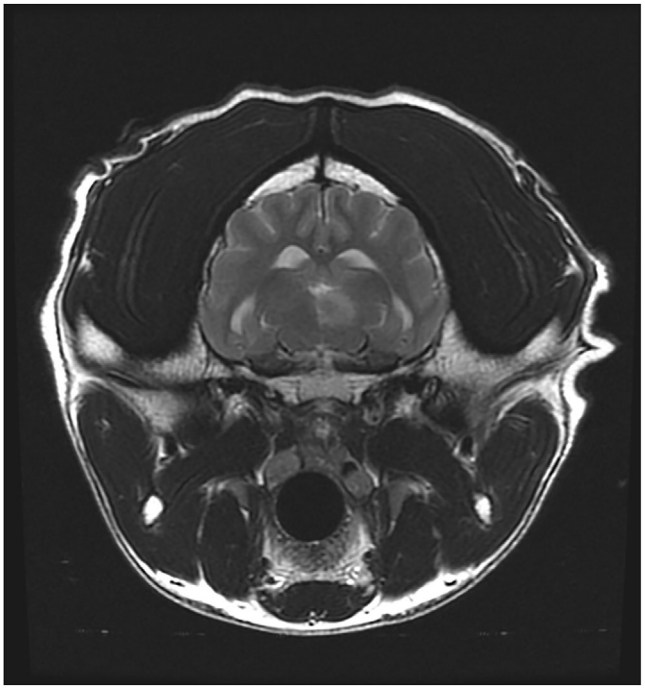

FIGURE 1a | T2W axial sequence at the level of the midbrain; pictured is a T2 mildly hypointense to isointense rounded lesion with perilesional T2 hyperintensity in the left dorsal midbrain.

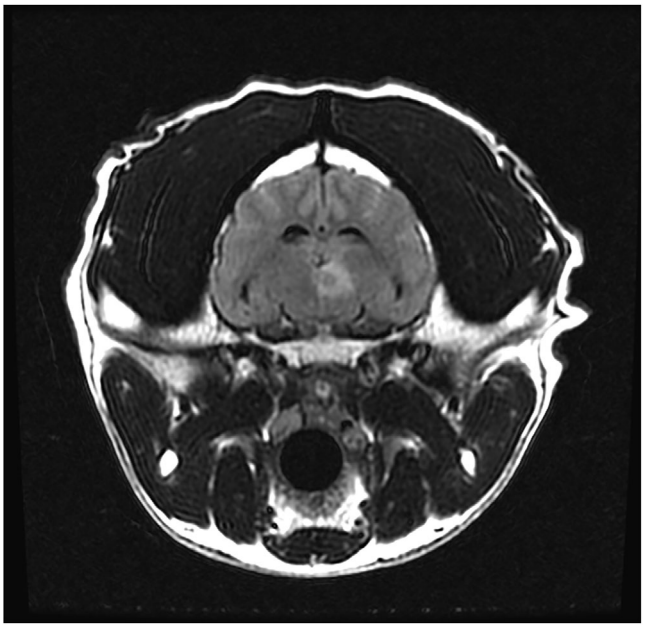

FIGURE 1b | FLAIR axial sequence at the level of the midbrain; illustrates that the perilesional intensity in Image 1a is also FLAIR hyperintense.

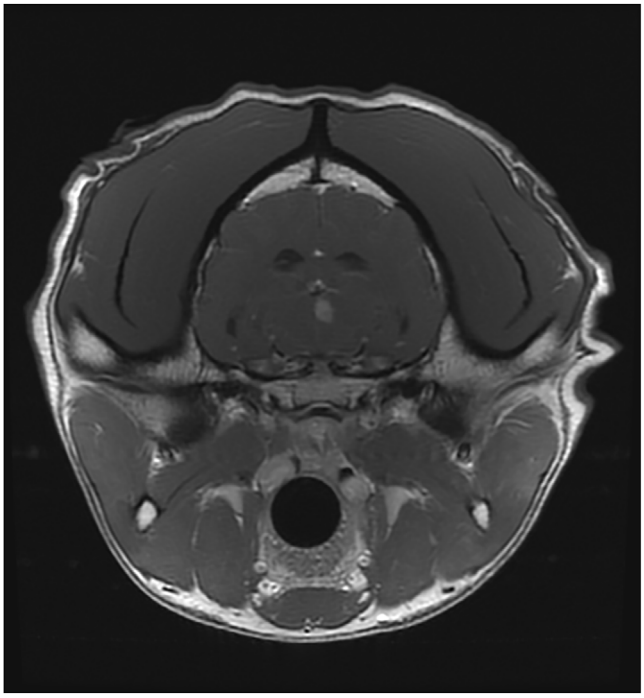

FIGURE 2 | T1W post-contrast axial sequence at the level of the midbrain; illustrates avid contrast enhancement of the dorsal midbrain lesion.

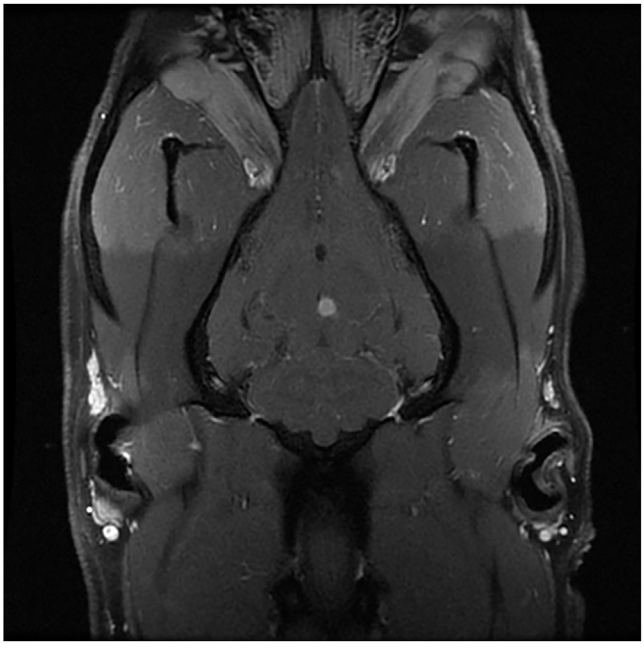

FIGURE 3 | T1W post-contrast dorsal sequence at the level of the dorsal midbrain.

and unstained CSF in the other chamber. White blood cells were counted from the stained sample after 10 min from time of preparation and the total number of visible cells multiplied by a factor of two to account for dilution. Red blood cells were counted as the total number of identifiable cells from the unstained sample, and the count of white blood cells was subtracted from the total count. There were four white blood

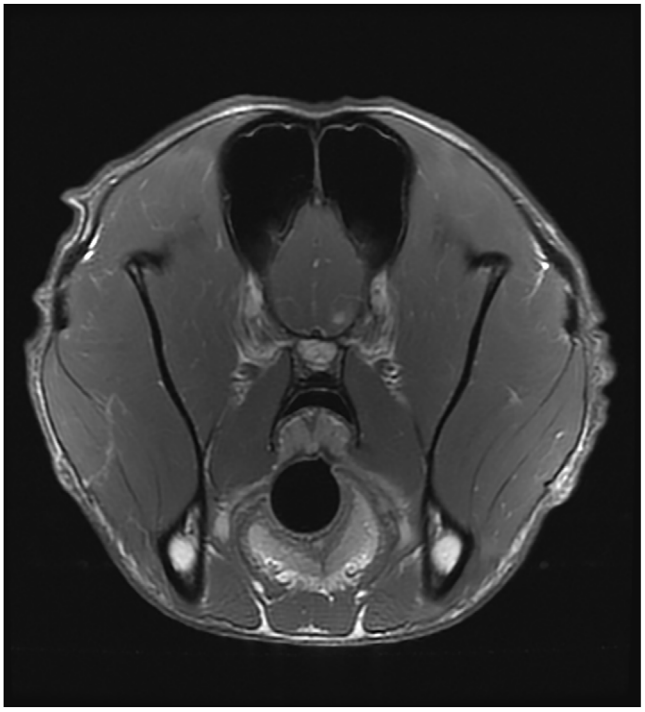

FIGURE 4 | T1W post-contrast axial sequence at the level of the rostral forebrain; illustrates an avidly contrast enhancing lesion in the left ventral frontal lobe similar in appearance to the midbrain lesion.

cells and zero red blood cells identified from the patient's CSF. Protein was measured using mass spectrography (Spectronic 200, ThermoFisher Scientific; Madison, WI) using manufacturer reagent protocols and measured 18 mg/dL. Cytospin preparations created were mostly acellular with scattered, occasional round cells, no erythrocytes, and minimal basophilic amorphous debris with few rafts of amorphous faintly basophilic material in the background. Round cells consisted predominately of small lymphocytes and plasma cells with a single instance of macrophagocytosis of a lymphocyte observed. Rare monocytes and a single foamy macrophage were also observed. Differential cell count was not performed due to low cellularity. No etiologic agents were observed. Final assessment was consistent with low-grade, mononuclear pleocytosis.

Based on imaging and CSF characteristics, infectious disease serology was extended to include *Rickettsia rickettsii, Cryptococcus neoformans, Toxoplasma gondii* and *Neospora caninum* (Protatek laboratories, Phoenix, AZ). Prednisone was prescribed at 0.94 mg/kg/day administered orally pending test results. Extended infectious screening was negative, but previously pending *C. immitis* test results returned positive for both IgG and IgM, with only IgG quantified via immunodiffusion titer at 1:16 (Idexx laboratories). Treatment was initiated with fluconazole orally at 9.4 mg/kg every 12-h, and within 48-h of starting prednisone and fluconazole the patient's abnormal globe movements abated. The patient further improved over the following ten days to have a more normal facial expression, with improved elevation of superior eyelids, and his energy levels had subjectively normalized based on owner observation. Over the next ten days, the prednisone dose was tapered to 0.3 mg/kg orally every 24-h without setback, then again to 0.3 mg/kg orally every 48-h for 2 weeks and

discontinued. Within 1 week after discontinuation of prednisone, the patient developed mild recurrence of convergence-retraction nystagmus that resolved after approximately 48-h resuming 0.3 mg/kg prednisone orally daily. A prolonged taper (0.3 mg/kg orally every 24-h for 3 weeks then 0.3 mg/kg orally every 48-h for 6 weeks then discontinued) successfully eliminated this clinical sign with no reported recurrence in convergence-retraction nystagmus at time of publication.

The patient had biochemistry and Coccidioides serology evaluated at various intervals for monitoring while taking fluconazole. Two months after diagnosis, the patient had a mild hepatopathy with alanine transaminase (ALT) elevated at 247 U/L (reference range 10–125 U/L), alkaline phosphatase (ALP) elevated at 454 U/L (reference range 23–212 U/L) and agar gel immunodiffusion (AGID) for *C. immitis* was positive for both IgM and IgG, quantified 1:2 and 1:4, respectively. Five and six months into treatment with fluconazole, the mild increases in ALT and ALP were improved (ALT 128–177 U/L, ALP 209–361 U/L) but persistent, so an abdominal ultrasound was performed. Liver changes were described as hepatomegaly with a heterogenous mottled appearance. Subsequent liver biopsy was performed, and histopathology showed moderate vacuolar hepatopathy with rare individual hepatocyte necrosis, lobular hyperplasia and moderate to multifocally severe centrilobular and periportal fibrosis. Hepatotoxicity induced by fluconazole was the top differential considered in absence of copper accumulation. Due to concern for impending liver failure with the current treatment plan, the patient was discontinued from fluconazole seven months from initial diagnosis and initiated on voriconazole 5.1 mg/kg by mouth every 12-h. He was also started on nutraceutical therapies for liver support (SAMe 562.5 mg/Silybin 205 mg daily, ursodiol 250 mg twice daily, Vitamin E 400 IU daily). Eight months after diagnosis, ALP was stable at 323 U/L and Coccidioides AGID IgM negative, IgG positive quantified 1:8. Repeat abdominal ultrasound showed resolved hepatic mottled appearance with persistent hepatomegaly.

Repeat brain MRI was performed ten months from initial diagnosis using the same acquisition parameters and sequences as the initial study. Imaging characteristics of the frontal lobe lesion were similar to the initial study, with a T2-hypointense, mildly contrast enhancing mass lesion and mild perilesional FLAIR and T2 hyperintensity, but the lesion was about 50% smaller measuring 1.6 mm (W) × 1.6 mm (H) × 3.6 mm (L). There was complete resolution of the previously observed T2-hypointense, avidly contrast-enhancing lesion in the midbrain. The patient was still in a clinical remission from his neurological disease with this treatment protocol 14 months from initial diagnosis, and his liver disease is being monitored and managed by a board-certified small animal internal medicine specialist. Resolving MRI changes in addition to resolution of neurological signs and improving Coccidioides titres while on antifungal therapy further supports a clinical diagnosis for Valley Fever rather than metastatic neoplasia in this patient (Video S1).

3 | Discussion

Convergence-retraction nystagmus is defined predominately in human medical literature as a spontaneous, irregular movement of the globes with retraction into the orbit and convergence that worsens during attempts at upward gaze (Feroze and Patel 2022; Shields et al. 2017). It is one feature of the triad of Parinaud's syndrome, otherwise known as dorsal midbrain syndrome, which includes impaired upward gaze and pupillary hyporeflexia (Feroze and Patel 2022; Shields et al. 2017). The efferent ophthalmic pathways for eye movement involve multiple brainstem nuclei and tracts that have both excitatory and inhibitory outputs, resulting in coordinated and intentionally directed eye movements in healthy animals and humans. Convergence-retraction nystagmus is a complex eye movement with many involved pathways and occurs due to a highly localized lesion of the midbrain, particularly the ventral pretectum, periaqueductal areas and medial longitudinal fasciculus (Crawford et al. 2016).

Although the complete pathophysiology is unclear, it is postulated that convergence-retraction nystagmus occurs secondary to damage of supranuclear fibers of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) resulting in disinhibition of convergence and divergence neurons (Feroze and Patel 2022, Shields et al. 2017). Extraocular muscles, particularly the medial rectus muscle, receive excessive and sustained stimulation which contribute to the involuntary, rhythmic, and spontaneous converging globe movements (Feroze and Patel 2022; Shields et al. 2017). Compromise of adjacent midbrain nuclei and pathways depends on the size and exact location of the primary lesion, and may result in retraction of the superior eyelids, known as Collier's sign, or vestibular dysfunction in some patients (Crawford et al. 2016). Collier's sign was present in our patient, but he did not experience vestibular dysfunction. There are two published reports on convergence-retraction nystagmus in veterinary patients, and published cases are further limited to presumed cerebrovascular accident of the dorsal midbrain in dogs (Crawford et al. 2016; Liatis et al. 2020). Similarly, dorsal midbrain lesions in human patients are mostly caused by ischemic or hemorrhagic vascular accidents. Aside from cerebrovascular etiologies, another major cause of convergence-retraction nystagmus or Parinaud's syndrome in human patients is secondary to pineal gland tumour, and, less commonly, obstructive hydrocephalus, multiple sclerosis plaque formation, cerebral venous thrombosis, toxoplasmosis and metastatic neoplasms (Ortiz et al. 2021; Menon et al. 2007).

Both canine and human cases of convergence-retraction nystagmus diagnosed with ischemic cerebrovascular accident have similar magnetic resonance imaging findings: T2-weighted and FLAIR hyperintensities within the dorsal midbrain and/or thalamus of varying size, often well demarcated foci that are iso- to hypointense on T1-weighted imaging and non-gadolinium contrast enhancing (Crawford et al. 2016; Wessmann et al. 2009; Kang et al. 2009). Contrasted to imaging characteristics of cerebrovascular accident, our patient's midbrain lesion was hypointense on T2-weighted and FLAIR imaging, isointense on T1-weighted sequences with strong, uniform gadolinium enhancement, and perilesional T2 and FLAIR hyperintensity. These imaging characteristics have been described in dogs with granulomatous Coccidioides encephalitis that were either presumptively diagnosed based on positive serological testing for antibodies against the fungal organism with positive response to antifungal therapy or definitively diagnosed based on organism identification from histopathology after surgical mass excision

(Kelley et al. 2021; Bentley et al. 2015). In our patient, the midbrain lesion also shared imaging characteristics with a second lesion within the frontal lobe, which is more consistent with infectious etiologies or metastatic neoplasia than cerebrovascular accident.

Incidence of disseminated Coccidioides to the central nervous system in dogs is not clearly identified in the literature, although clinical, histopathologic, and imaging features of CNS infection have been well-documented. Kelley et al. described the MRI findings of 45 dogs who were presented for evaluation of acute neurological dysfunction localizing to brain and/or cranial cervical spine (Kelley et al. 2021). To be included in the study, all patients were required to have positive immunodiffusion titerr for *Coccidioides* and head MRI. Most cases (37/45) had lesions described as 'distinct, intra-axial, strongly and homogenously contrast-enhancing foci with mild to extensive surrounding T2-weighted hyperintensity consistent with perilesional edema' (Kelley et al. 2021). This was referred to as the 'granulomatous form' and described intra-axial mass lesions like those in our patient. Granulomatous fungal mycosis within the CNS is similarly described in both human and veterinary literature (Mishra et al. 2019).

The gold standard for diagnosis of coccidioidomycosis in both human and veterinary medicine requires organism identification in tissues, which is not always possible due to inaccessibility of lesions deep within the body or in delicate tissues (Graupmann-Kuzma et al. 2008). In human patients with Valley Fever CNS infection, cerebrospinal fluid analysis can contribute to a definitive diagnosis with both non-specific inflammatory changes like lymphocytic or eosinophilic pleocytosis and positive Coccidioides complement-fixation antibody testing (Bamberger et al. 2015, Jackson et al. 2019). In 2021, Butkiewicz et al. published findings on both antigen and antibody detection in cerebrospinal fluid in canine patients with CNS coccidioidomycosis, but found only about 20%–46% sensitivity in dogs contrasted with 93% sensitivity in human patients (Butkiewicz et al. 2021). Although a mild mononuclear pleocytosis was detected in our patient, CSF Coccidioides assays were not pursued. Instead, a presumptive diagnosis based on imaging characteristics, serological testing results and response to treatment with antifungal medication were considered together to yield a presumptive diagnosis of coccidioidomycosis for our patient. A presumptive diagnosis made using these criteria is the most common in most veterinary patients afflicted with CNS disseminated disease (Kelley et al. 2021; Davidson et al. 2019). Repeat brain MRI performed ten months after diagnosis showed resolution of the previous midbrain lesion as well as 50% reduction in size of the frontal lobe lesion; improvement in both clinical signs and imaging after treatment with antifungal medication further supports a diagnosis of Coccidioidomycosis over metastatic neoplasia.

To the authors' knowledge, this is the first report describing convergence-retraction nystagmus caused by intracranial *Coccidioides immitis* in a dog. Our findings highlight the specific localization of an intracranial lesion as it relates to the clinical sign of convergence-retraction nystagmus and emphasizes the importance of including differential diagnoses aside from vascular accident, despite vascular etiologies being the most reported causes of convergence-retraction nystagmus in the dog.

Author Contributions

Concept and Design: Lydia Lovato. Acquisition of Data: Lydia Lovato, Trevor Moore and Jaime Sage. Analysis and Interpretation of Data: Lydia Lovato and Trevor Moore. Revising Article for Intellectual Content and Final Approval: Lydia Lovato, Trevor Moore, Laura Stainback, Scott Plummer, Kim Knowles and Jaime Sage.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Patient data are accessible through Veterinary Neurological Center patient database.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/vms3.70249.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.