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Clinical characteristics, magnetic resonance imaging features, treatment, and outcome for presumed intracranial coccidioidomycosis in 45 dogs (2009-2019)

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Abstract

Background: Knowledge of the clinical and magnetic resonance imaging (MRI) features of intracranial *Coccidioides* infection in dogs is essential for prompt diagnosis to limit disease-associated morbidity and death.

Objectives: To describe the MRI appearance of intracranial coccidioidomycosis in dogs, identify associated clinical and clinicopathologic findings, and report outcomes of medical treatment.

Animals: Forty-five client-owned dogs with presumed intracranial *Coccidioides* infection.

Methods: Retrospective case series. Medical records and images were reviewed. Clinical history, examination findings, serology, imaging characteristics, treatment, and outcome were recorded. Included cases had an abnormal brain MRI and positive *Coccidioides* serology by agar-gel-immunodiffusion (AGID).

Results: Median age was 7-years. Generalized tonic-clonic seizures were the most common presenting sign (25/45). Two lesion categories were identified: a granulomatous form with 1 or more distinct, intra-axial, contrast-enhancing foci (37/45), and a second variation with diffuse, bilateral, symmetrical lesions of the caudate nuclei and frontal lobes (8/45). Serum IgG titers ranged from 1 : 1 to ≥ 1 : 256; 2 dogs had positive IgM titers at 1 : 2. All dogs with follow-up serology (34/45) had a reduction in titer. Mean duration of follow-up was 22.4 ± 20.5 months (median 16 months). Six dogs were lost to follow-up <1-year after diagnosis (median 9 months). Five dogs were clinically well but had yet to be followed for >1-year. Of the remaining 34 dogs, 28 (82%) were alive ≥ 1-year after diagnosis. Thirteen of these dogs had follow-up times ≥ 2-years.

Conclusions and Clinical Importance: The prognosis for intracranial *Coccidioides* infection is generally more favorable with medical treatment than in earlier reports.

KEYWORDS
canine encephalitis, coccidioidomycosis, fungal meningoencephalitis, valley fever

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1 | INTRODUCTION

Disseminated coccidioidomycosis causes substantial morbidity, particularly when involving the central nervous system (CNS).[1-5] Once in the brain, if left untreated, the infection is invariably fatal.[6] Subclinical disease can linger for months to years before dissemination.[1,3] Thus, recognition of infection is relevant to all clinicians and not just those in endemic regions.[1,6-8] Diagnosis in dogs is complicated by lack of a sensitive antigen test, relative frequency of seronegative disease, and fact that positive titers do not distinguish active disease from prior exposure.[1-3,8,9]

Coccidioidomycosis occurs in numerous species, and infections in dogs might serve as sentinels for human exposure.[2,10] Most infections are subclinical, and only a minority of dogs develop disseminated disease.[2,3,5,11-13] Dissemination rate in dogs is suspected to be higher than the 1/500 cases reported in humans.[14,15] The time between infection and evidence of dissemination ranges from several weeks to several years.[1,7,8] Clinical signs reflect the primary organ system(s) involved.[1-3,10,11] A history of respiratory signs might or might not be present.[1-3] In 1 study, 22% of dogs with disseminated infection had no previous respiratory illness.[3] The most common manifestations of disseminated infection are lameness from osteomyelitis in dogs and dermatologic disease in cats.[1,3,7,11,15,16] Clinicopathologic abnormalities might include hypoalbuminemia, hyperglobulinemia, neutrophilia, and monocytosis.[1-5,13] Serology by agar-gel immunodiffusion (AGID) or ELISA could support the diagnosis. However, there is overlap in low-positive IgG titers among clinical and subclinical infections in dogs, and clinically relevant disease can occur in the absence of seroconversion.[1,3,4,11,15] The incidence of seronegative disease in dogs is estimated to be 5% to 10% in regions in which the disease is endemic.[4,5]

Dissemination to the CNS in dogs most commonly involves the cerebrum.[4,11] In humans, CNS infection typically causes a diffuse or basilar meningitis, while intracranial lesions in dogs are more often focal granulomatous masses.[4,6,7,11,15,17] Although individual case reports of focal intracranial *Coccidioides* granulomas exist in the human literature, the prevalence of focal brain lesions is rare in people compared to dogs.[18] There remains sparse information available describing the clinical characteristics, magnetic resonance imaging (MRI) findings, and prognosis for dogs with disseminated *Coccidioides* infection involving the CNS.[1,15] Previous reports have focused primarily on atypical variations of the disease and comprise single case reports or findings within a small subset of dogs.[1,4,7,11,17,19] The objective of this study was to characterize the clinical and MRI features of intracranial *Coccidioides* infection in dogs and to assess outcomes with medical treatment.

2 | MATERIALS AND METHODS

This was a retrospective case series approved by the hospital administrator for the Veterinary Neurological Center in Phoenix, Arizona. The aim was to describe the presenting signs, clinicopathologic and MRI findings, and outcomes of dogs with intracranial *Coccidioides immitis* infection. The medical record database was searched with terms including coccidioides-intracranial, coccidioides-encephalitis and coccidioides-granuloma between the years 2009 and 2019.

Dogs were selected for inclusion if they had an abnormal brain MRI in conjunction with positive serology for *C. immitis* and complete medical record data available for review. Cerebrospinal fluid (CSF) analysis was not required as many dogs had not undergone this test based on extensive brain edema with associated mass effect and presumptive high risk. Alive and dead dogs were included to evaluate outcome. Cases were excluded if images could not be accessed via the hospital database at the time of writing. Positive *Coccidioides* serology (IgG ≥ 1 : 1) by AGID performed ≤1-month before (median 3.5 days, mean 11.6 ± 3 days; 16/45 dogs) or at the time of MRI (29/45 dogs) was required in all cases. The laboratory was not standardized: testing was performed through ProtaTek laboratory (Mesa, Arizona) for 34/45 (76%) dogs, Antech laboratory (Phoenix, Arizona) for 7/45 dogs (15%), and Idexx laboratory (Phoenix, Arizona) for 4/45 dogs (9%). Seronegative cases (IgG < 1 : 1) were excluded to reduce the risk of inadvertently including dogs with a different disease process because histopathologic confirmation of infection was lacking.

Each dog's signalment, medical history, clinical signs, examination findings, hematologic and clinicopathologic results, *Coccidioides* serology, other infectious disease serology, MRI description, CSF results, treatment, and outcome were recorded. Any history of extraneural signs suggestive of coccidioidomycosis was noted, including cough, lymphadenopathy, osteomyelitis, or pyrexia. Clinicopathologic abnormalities supportive of systemic inflammation or infection, including hyperglobulinemia (>4.0 g/dL), neutrophilic leukocytosis (WBC >16 k/μL, neutrophils >12 k/μL), and monocytosis (≥1.2 k/μL), were evaluated. Serology at the time of imaging was recorded. Results of repeat serology and repeat MRI were reported when available. The time to most recent follow-up, death, or euthanasia was recorded. Information regarding outcome was obtained from medical records and telephone conversations with referring veterinarians. Owners were contacted only if the dog was known to be living based on a recent neurology recheck exam or primary care visit and approval was attained from the institutional review board for the Veterinary Neurological Center.

Each dog's MRI was reviewed by a neurology resident and an ACVIM-boarded neurologist using an image analysis workstation (eFilm, Workstation-v.2.1.2; Merge Healthcare) and the findings reported. Descriptive statistics were calculated using a spreadsheet data analysis software (Microsoft Excel, 2020-v.16.40).

3 | RESULTS

Search of the medical records database identified 123 cases of *Coccidioides* encephalitis between 2009 and 2019. Seventy-nine dogs were identified in the initial search. Twelve were excluded because of inability to access the MRI studies using the current hospital imaging software. One case was excluded because of lack of serology. An additional 21 cases were excluded because of negative serum titers, for a total of 45 dogs included in the study (Figure 1). Follow-up MRI
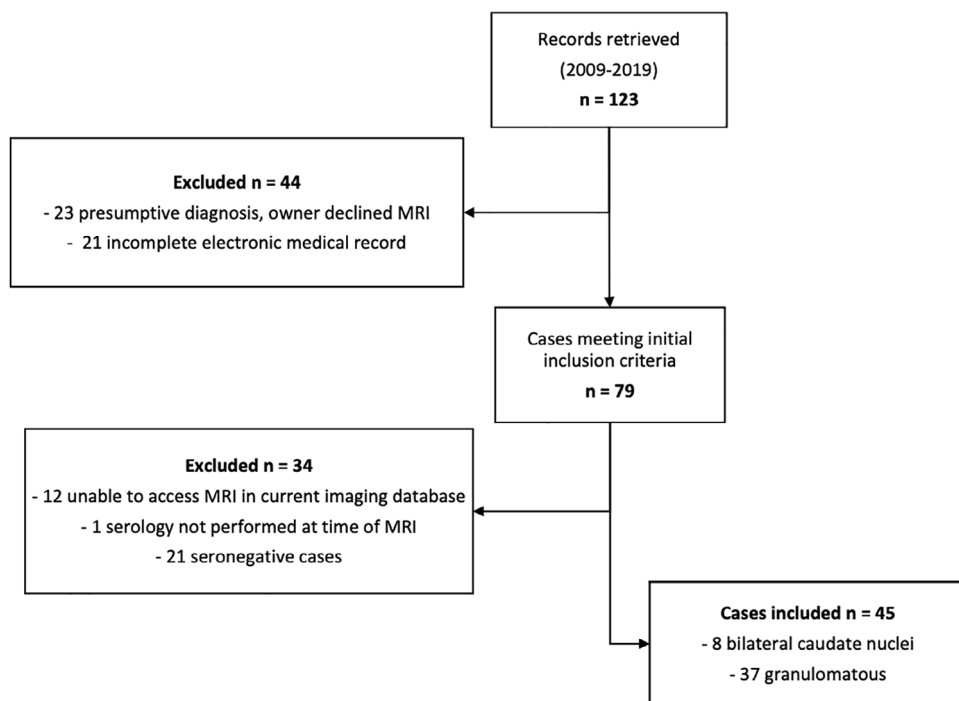
was available for 11/45 dogs (24%). Follow-up serology was available for 34/45 dogs (76%). The signalment, findings and outcome for each case are summarized in Table S1.

There were 25 neutered males, 2 intact males, and 18 spayed females. Ages ranged from 1.5 to 13 years (median 7 years). Body weight ranged from 5.3 to 56.8 kg (median 23.7 kg). There were 5 Miniature Schnauzers, 3 Labrador Retrievers, 3 Dachshunds, and 2 Golden Retrievers. The remaining 32 dogs were of various pure and mixed breeds.

The most common presenting complaint, present in 25/45 dogs (56%), was an acute onset of generalized tonic-clonic seizures. Of these, acute onset of generalized cluster seizures occurred in 14/25 dogs and 2 dogs presented with status epilepticus. Other presenting complaints included acute onset vestibular signs (7/45), compulsive circling (4/45), head pressing (3/45), behavioral changes (2/45), acute hemiparesis or tetraparesis (2/45), cervical pain (1/45), and generalized hyperesthesia (1/45).

Twenty-seven of the 45 dogs (60%) had a history of systemic signs suspected to be from *Coccidioides* infection. Duration of time lapsed from systemic signs to presentation ranged from 3 weeks to 2 years, consistent with previous reports.[1,7,8] There was a history of nonproductive cough in 16/45 dogs, osteomyelitis in 1 dog, and hilar lymphadenopathy on radiographs in 2/45 dogs. Eight dogs had an elevated rectal temperature (≥102.6 °F) before referral or at the time of consultation which could not be explained by recent seizure activity. Seventeen dogs (17/45) had been previously treated with fluconazole. Treatment was discontinued in 4 dogs before evaluation, with 1 dog having stopped the drug 2.5 weeks prior, 1 dog 8 months prior, and the time since drug cessation was not documented for 2 dogs. Thirteen dogs were receiving fluconazole at the time of evaluation; however, 1 dog was taking the drug only once daily, 7/13 dogs were being

treated with compounded formulations, 2/13 dogs had been taking the medication for only 4 days, and the dose, formulation, and treatment duration were unclear in the medical record for the remaining 3 dogs.

Physical and neurologic examinations were performed by a neurology resident or an ACVIM board-certified neurologist, or both. Hyperthermia was identified in 8/45 dogs (median 102.9 °F, range, 102.7-104.6 °F). Neurological deficits included an asymmetrical menace response deficit (16/45), compulsive circling or a tendency to circle toward a particular direction (8/45), hemiparesis (7/45), central vestibular signs (7/45), and asymmetrical facial hypalgesia (4/45). Complete blood count and biochemistry data before MRI and treatment were available for 37/45 dogs. A hyperglobulinemia was present in 13/37 dogs (median 4.6 g/dL, range 4-6.1 g/dL). A neutrophilia was noted in 11/37 dogs (median 15.6 k/μL, range 12.3-20.7 k/μL), and a monocytosis was identified in 3/37 dogs (median 1.29 k/μL, range 1.2-1.9 k/μL).

All dogs had positive IgG titers; 2 dogs had a concurrently positive IgM titer at 1 : 2. Positive IgG titers ranged from 1 : 1 to ≥ 1 : 256 (Figure 2). Other infectious diseases serology was performed in 24/45 dogs (53%; Table S2). *Cryptococcus neoformans*, *Toxoplasma gondii*, and *Neospora caninum* serology was performed in 4/45 dogs and was negative. Two of these dogs were also seronegative for *Ehrlichia canis*. *Ehrlichia canis* serology was performed in an additional 20/45 dogs, 2 of which had positive IgG titers. Two of these dogs had a history of ehrlichiosis and treatment 3 to 4 years before MRI with persistently positive titers. Blood PCR for tick-borne pathogens was performed in 1 of these dogs and was negative. The third dog with positive *E. canis* serology showed a low IgG titer of 1 : 25. This dog was treated only for coccidioidomycosis and had a favorable outcome, with complete lesion resolution on repeat MRI 84-months later.

Cerebrospinal fluid was obtained from 4/45 dogs. Samples were collected from the cerebellomedullary cistern immediately following MRI. Median protein content was 81.9 mg/dL (range, 46-114 mg/dL). Median cellularity was 12 WBC/mm^3 (range, 2-314 WBC/mm^3). Of the 2 samples with a pleocytosis, both demonstrated pyogranulomatous inflammation.

Head MRI was performed under general anesthesia with propofol and isoflurane using a 1.0 or 1.5 Tesla magnet (GE Healthcare; Milwaukee, Wisconsin). Imaging protocol varied; however, all cases included T2-weighted and T1-weighted transverse pre- and postcontrast sequences acquired as fast spin echo. Thirty-one cases (31/45) also included sagittal T2-weighted and T1 postcontrast and transverse T2-FLAIR, T2*-GRE, and diffusion-weighted images. Average slice thickness was 4 mm with a 0.5 to 1 mm interslice gap. T1-weighted

postcontrast images were obtained following intravenous injection of .2 mL/kg gadobenate dimeglumine (Multihance, Bracco Diagnostics, Inc).

Two distinct categories of lesions were identified on MRI: a granulomatous form and a second variation resulting in diffuse, bilaterally symmetrical lesions of the caudate nuclei and frontal lobes. The majority of cases (37/45) revealed 1 or more distinct, intra-axial, strongly and homogeneously contrast-enhancing foci with mild to extensive surrounding T2-weighted hyperintensity consistent with perilesional edema (Figure 3). A single granuloma was present in 35/37 dogs, while 2/37 dogs had multiple granulomas. The remaining 8 cases were reported in a previous study.[4] These dogs had bilaterally symmetrical lesions of the caudate nuclei and frontal lobes which were T2 and FLAIR hyperintense, T1 iso- to hypointense and either lacked contrast enhancement (3/8) or had faint, wispy enhancement of the lesion and adjacent meninges (5/8). One dog also had evidence of focal ischemic infarction within the caudate nucleus as evidenced by positive diffusion-weighted imaging and confirmed on apparent diffusion coefficient mapping.[4]

Of the identified granulomas, most lesions were supratentorial (29/37). Eight dogs had lesions within the brainstem or cerebellum. Granulomas ranged in size from 1 to 17 mm at their largest extent (median 7 mm) and were predominantly T2-weighted hypointense (32/37) and T1-weighted isointense (34/37) compared to normal gray matter (Figure 3). Edema was mild in 5/37 dogs, moderate in 16/37 dogs, and severe in 16/37 dogs. A mass effect, characterized by a midline shift, or subtentorial, subfalcine, or foramen magnum herniation, or both, was present in 13/37 dogs. Intense contrast enhancement of the meninges adjacent to the lesion was seen in 9/37 dogs, with a dural tail present in 2/9 cases. Obstructive hydrocephalus was diagnosed in 1 dog on initial MRI and 1 dog on repeat
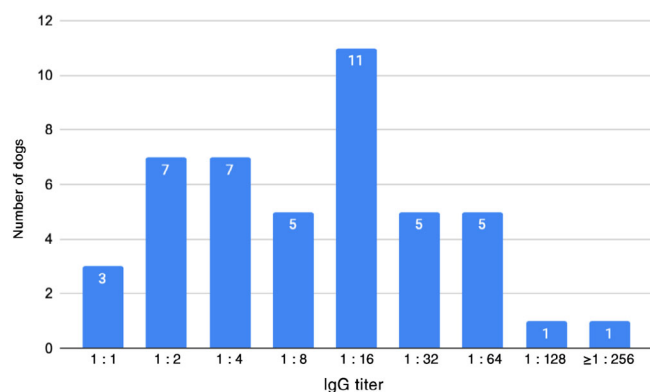

FIGURE 2 IgG *Coccidioides* antibody titers by agar-gel immunodiffusion (AGID) for 45 dogs
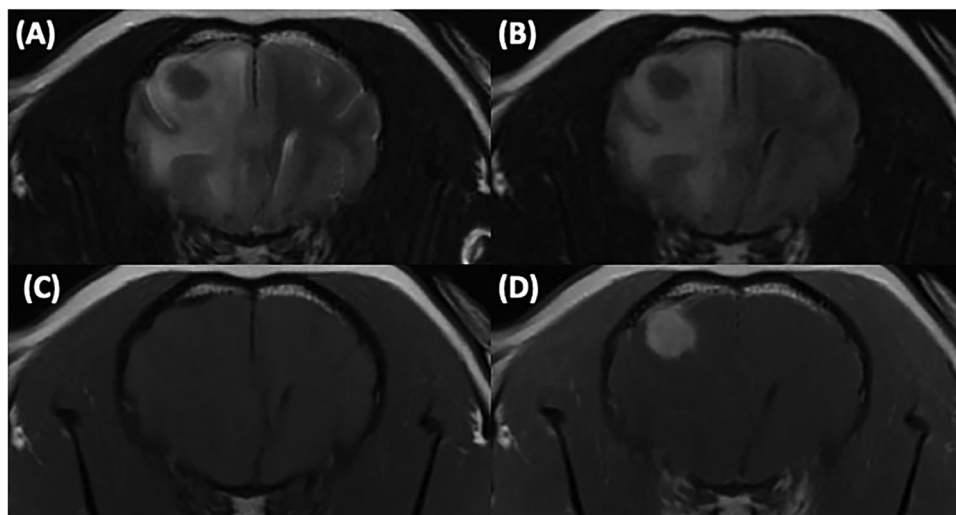

FIGURE 3 Brain MRI of a 13-year-old neutered male Dachshund with lethargic mentation, episodes of decreased responsiveness and staring off into space, and cervical pain. *Coccidioides* serology at diagnosis was IgG positive at 1 : 32. A, Transverse T2-weighted image. B, Transverse T2-FLAIR. C, Transverse T1-weighted image. D, Transverse T1-weighted postcontrast. Note the extensive T2 and FLAIR hyperintensity consistent with severe perilesional edema. Within this hyperintense region is a focal intraparenchymal mass lesion that is T1-weighted isointense and strongly, homogeneously contrast-enhancing. The left side of the image corresponds to the right side of the cranium. MRI, magnetic resonance imaging; FLAIR, T2-fluid attenuated inversion recovery
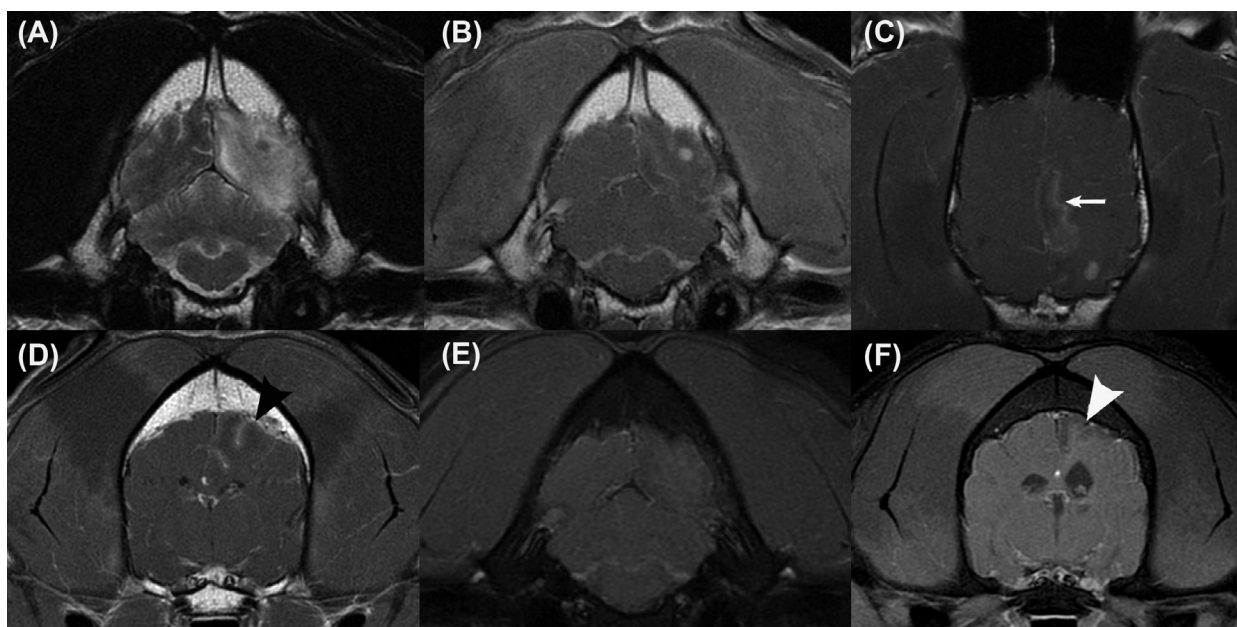
FIGURE 4 Brain MRI of a 2-year-old neutered male Cane Corso at the time of diagnosis (A-D) and 7 months later (E and F). The dog presented with severe cluster seizures. Serology at diagnosis was IgG positive at 1 : 2; follow up titers were negative. Repeat MRI was performed because of recurrent seizures. A, Transverse T2-weighted and B, transverse T1-weighted postcontrast images show a focal, strongly contrast-enhancing lesion within the left occipital lobe with surrounding edema. C, Dorsal T1-weighted postcontrast image shows enhancement of the primary lesion with additional linear enhancement of the adjacent cortical gray matter (white arrow). D, Corresponding T1-weighted postcontrast image at the level of the thalamus showing gadolinium enhancement along a rim of gray matter cranial to the location of the primary lesion (black arrowhead). E, Transverse T1-weighted postcontrast with fat-saturation at the level of primary lesion and F, cranially at the level of the thalamus. The fungal granuloma within the left occipital lobe has resolved. The rim of gray matter that previously enhanced postgadolinium is now T1-weighted hypointense consistent with cavitation secondary to laminar cortical necrosis (white arrowhead). The left side of the image corresponds to the right side of the cranium. MRI, magnetic resonance imaging

imaging. In the latter case, evidence of ventriculitis was seen on the initial MRI.

In 2 dogs, there was additional focal, linear gadolinium enhancement along a rim of cerebrocortical gray matter suggestive of laminar cortical necrosis which persisted on follow-up imaging in 1 dog (Figure 4).[20] In both dogs, prolonged or refractory seizure activity was noted in the history. One other dog had osteomyelitis of the right zygomatic arch, with visible osteolysis and intense contrast-enhancement of this region. Cerebrovascular infarction was present in 2 dogs. One of these dogs had concurrent hypothyroidism and unilateral ischemic lesions in the caudate nucleus and thalamus; the second dog, also with ischemic infarction of the caudate nuclei, had the bilaterally symmetrical encephalitic form of infection.

3.1 | Treatment

All cases were treated with medications to reduce cerebral edema, including intravenous administration of mannitol, hypertonic saline, dexamethasone sodium phosphate, or a combination of these drugs. The dose of dexamethasone, when administered, ranged from 0.01 to 0.5 mg/kg (median 0.24 mg/kg). All dogs were discharged on fluconazole and anti-inflammatory doses of prednisone (median 1 mg/kg/d), with initiation of gradual tapering after 7 to 10 days. Duration of

corticosteroid treatment was recorded for 25/45 dogs. Mean duration of prednisone taper was 2.6 ± 1.8 months (median 2-months). Fluconazole doses ranged from 5.3 to 11.3 mg/kg PO q12h (median 9.4 mg/kg q12h). Generic fluconazole or Diflucan was recommended in most cases. Seven dogs were receiving compounded fluconazole at a therapeutic dose (range, 5.7-10.9 mg/kg q12h) for between 1-week and 5-months (mean 2 ± 1.8 months, median 1-month) at the time of MRI and were changed to a generic formulation at an equivalent dosage. Anticonvulsants were prescribed when indicated. Levetiracetam was used most frequently because of risk of hepatotoxicosis from combining fluconazole with phenobarbital or zonisamide. Denamarin or SAMe-LQ was recommended in most cases for liver support because of the need for long-term fluconazole treatment. Fluconazole was discontinued in a single dog after 60-months of treatment and 3 consecutive negative serum titers. This dog was rechecked at 84-months, at which time neurologic examination was normal and repeat MRI showed complete lesion resolution.

3.2 | Outcome

Mean duration of follow-up was 22.4 months (median 16-months, range, 1-89 months). Six (6/45) dogs were lost to follow-up <1-year after diagnosis (median 9-months, range 2-11 months); these dogs
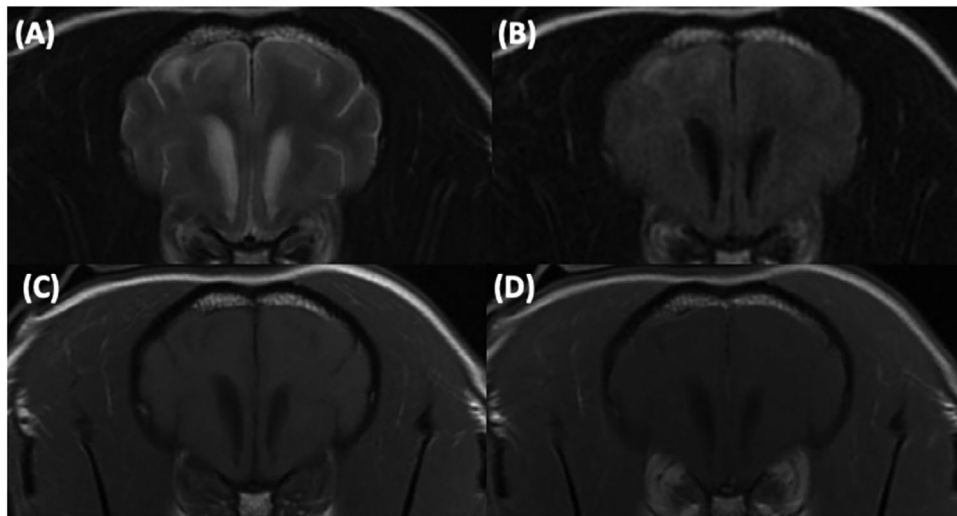
FIGURE 5 Repeat brain MRI of the same dog as in Figure 3 performed 18 months later. Repeat serology throughout the course of treatment showed a gradual decline in IgG titer, though the dog remained seropositive at IgG 1 : 4. A, Transverse T2-weighted image. B, Transverse T2-FLAIR. C, Transverse T1-weighted image. D, Transverse T1-weighted postcontrast image. There is nearly complete resolution of the fungal granuloma and associated edema. The left side of the image corresponds to the right side of the cranium. MRI, magnetic resonance imaging; FLAIR, T2-fluid attenuated inversion recovery
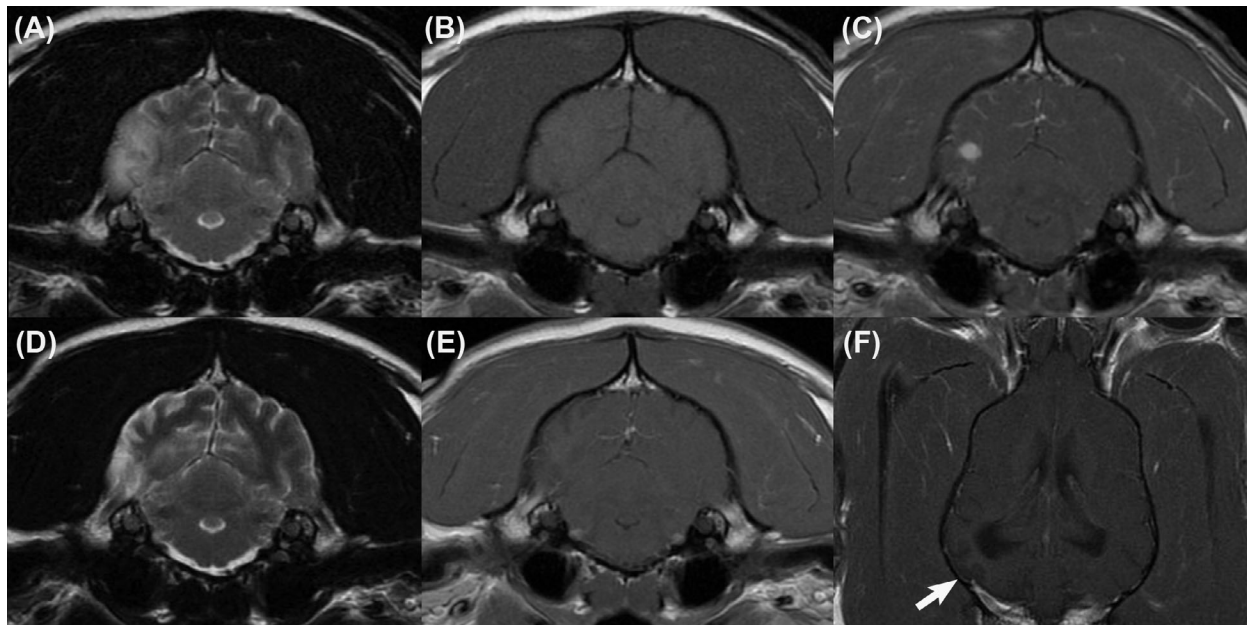

FIGURE 6 Brain MRI of a 2-year-old neutered male Labrador Retriever at the time of diagnosis (A-C) and 17 months later (D-F). The dog presented with cluster seizures, compulsive circling, and a menace response deficit. The initial IgG titer was 1 : 16. Follow up serology showed a decreasing titer, with IgG 1 : 2 at the time of repeat MRI. A, Transverse T2-weighted image. B, Transverse T1-weighted image. C, Transverse T1-weighted postcontrast image. There is a focal, intra-axial, T2 hypointense, T1 isointense lesion within the right occipital cortex that is strongly, homogenously contrast-enhancing with mild associated perilesional edema. D, Transverse T2-weighted and E, T1-weighted postcontrast images 17 months following initiation of treatment for intracranial coccidioidomycosis. The fungal granuloma and secondary edema are no longer present. F, Corresponding dorsal T1-weighted postcontrast image. The previous lesion has been replaced by cerebrospinal fluid (arrow). The left side of the image corresponds to the right side of the cranium. MRI, magnetic resonance imaging

were not included in evaluation of long-term survivability. Survival data is reported for the remaining 39/45 dogs, with 28 dogs alive at the time of writing. Three (3/39, 8%) dogs failed to survive >1-month after diagnosis. One of these dogs was euthanized because of severe hepatotoxicosis from combination treatment with fluconazole, phenobarbital, and carprofen before referral; 1 dog was euthanized at owner

request because of a concurrent nasal lesion presumed to be neo-plastic, although histopathology was not performed to definitively exclude a possible fungal etiology; the cause of death was unclear for the remaining dog. Three (3/39, 8%) dogs died or were euthanized >1-month but <1-year after MRI (range, 3-8 months). Two of these dogs died because of acute neurological deterioration; cardiopulmo-nary arrest secondary to obstructive hydrocephalus and foramen mag-num herniation was the suspected cause of death in both dogs. Repeat head MRI in 1 of these dogs 4-months after diagnosis showed a resolving fungal granuloma but persistent meningeal enhancement, suggestive of ongoing inflammation, and an obstructive hydrocephalus causing ventricular enlargement and midbrain compression. The owners were unable to pursue ventriculoperitoneal shunt placement, and the dog passed away from respiratory arrest 2.5 months later. For the remaining dog, the cause of death was unclear. Two dogs (2/39, 5%) were euthanized between 12 and 24 months after diagnosis: 1 because of hepatic failure presumably associated with combination drug therapy, and the second from development of a progressive men-ingitis. Three dogs (3/39, 8%) died or were euthanized >24 months after diagnosis, including 1 at 33-months from pyelonephritis, 1 at 52-months from an intradural extramedullary mass suspected to be a meningioma, and 1 at 72-months from an unstated cause.

Of the 28 dogs alive at the time of writing, all were clinically doing well. Five dogs (5/28, 18%) had a follow-up duration of >1-month but <1-year (median 10-months). Ten (10/28, 36%) were alive with follow-up ranging from 12 to 23 months. Seven (7/28, 25%) were alive with follow-up between 24 and 35 months, and 6 dogs (6/28, 21%) were alive with follow-up exceeding 36-months (range, 36-89 months).

Results of repeat serology were available for 34/45 dogs. A nega-tive titer was documented at follow-up in 11/34 dogs (32%) in response to treatment. Initial titers at the time of diagnosis for these 11 dogs ranged from IgG 1 : 2 to 1 : 32. A reduction in serum titer was identified in the remaining 23/34 dogs (68%), with follow-up titers ranging from 1 : 1 to 1 : 32 (median 1 : 4).

Repeat MRI was performed in 11/45 dogs (24%) between 4 and 84 months after diagnosis (median 12-months). Complete resolution of the initial brain lesion and secondary edema was documented in 8/11 dogs (73%) in response to treatment. In the remaining 3/11 cases, there was a substantial reduction in lesion size and severity of associated edema (Figure 5). In 5 of the 8 dogs with complete resolu-tion, there was distinct replacement of the previous lesion with a cerebrospinal fluid-filled void (Figure 6). The duration of time between initial and repeat imaging was generally longer for dogs with complete resolution (median 14.5 months, range 7-84 months) compared to those with residual lesions (median 5-months, range 4-18 months).

4 | DISCUSSION

This retrospective case series describes the clinical and MRI character-istics and outcome for 45 dogs with intracranial coccidioidomycosis. Presumptive diagnosis was made by positive *Coccidioides* serology and abnormalities on brain MRI. Although histopathology is the gold

standard to obtain a definitive diagnosis, cost to the client and poten-tial morbidity associated with this procedure limit its use in private clinical practice. In the current study, repeat serology, repeat brain MRI, or both were used when possible to document the dog's response to therapy and support the presumptive diagnosis.

In dogs, CNS *Coccidioides* infection most commonly affects the cerebrum, and a sudden onset of generalized tonic-clonic seizures with a high tendency toward cluster seizures was the most common clinical presentation in our and in other reported studies.[15] Brain lesions often manifest as single or, less commonly, multiple, intraparenchymal, well-circumscribed, strongly contrast-enhancing granulomas, as seen in 82% (37/45) of the cases reported herein.[15] A secondary form, manifesting as bilaterally symmetrical T2 and FLAIR hyperintensity within the cau-date nuclei and frontal lobes occurs and was seen in 8/45 cases (18%) in the current study.[4] This secondary form has a strong breed-predilection for Miniature Schnauzers.[4] This differs from the basilar and diffuse meningitis typical in humans with intracranial coccidioido-mycosis.[11,15,21,22] Intra-axial granulomatous mass-type lesions in the brain in people primarily involve immunosuppressed individuals.[18,23] Unlike in humans, dogs with intra-axial fungal granulomas might be immunocompetent.[1]

Diagnostic laboratory tests for *Coccidioides* infection can aid in the diagnosis of infection but do not always provide a definitive answer regarding active infection. Assays for antigen detection in serum and urine exist and are relatively sensitive and specific for *Coccidioides* infection in humans, but previous investigation of their use in dogs reports a sensitivity of ≤20%.[2,9] For this reason, testing for *Coccidioides* antigen is not typically performed in dogs, particularly given the added cost for such testing with a known low diagnostic yield. Serum AGID for anti-*Coccidioides* antibodies is fairly sensitive, though not all dogs with clinically significant disease show positive titers.[1,3-5,15] Five to ten percent of dogs with clinically relevant dis-ease are seronegative, further supporting the importance of recogni-tion of imaging findings consistent with valley fever in light of the generally positive response to therapy in these dogs.[4,5] No dogs with negative serology were included in the current study to reduce reporting error.

The degree of titer elevation does not necessarily correlate with the severity of clinical disease, particularly with primary CNS disease. In human patients, an IgG titer of ≥ 1 : 16 is reported as consistent with active infection for diagnosis of *Coccidioides* osteomyelitis and cutaneous lesions.[6,9] However, for CNS lesions, IgG titers of ≤ 1 : 16 were reported to be relatively common in human patients with CNS infection.[6,9]

In our study group, nearly half (22/45, 49%) of dogs had IgG titers ≤ 1 : 8, with the majority of these measuring 1 : 4 or lower (17/22, 77%). As antibody titers are indicative of a host's immune response to infection, it could be suggested that a low or negative titer along with disseminated disease might represent a deficient immune response in these dogs. However, defense against fungal organisms primarily involves cell-mediated rather than humoral immunity.[8,14,19] It might also be argued that a low serum antibody response reflects the biolog-ical nature of the CNS as an immunoprivileged site because the

majority of dogs with intracranial disease were not showing systemic signs at the time of diagnosis. As suggested by a previous case report in which fungal granulomatous lesions were isolated to the brain, it is possible that sequestration of antigen within the CNS might prevent an adequate serum antibody response.[19] Only 2 dogs in the current study had a positive IgM titer, which is not unexpected given the biological progression of antibody development and the time required for dissemination to occur, as IgM levels rise earlier in the disease course and subsequently dissipate over weeks to months.[12,13] In contrast, IgG levels rise shortly after IgM and persist for much longer.[12,19] Our findings agree with those of a previous investigation, in which only 1/13 dogs with intracranial coccidioidomycosis had a positive IgM titer at the time of MRI.[4] Other clinicopathologic findings in this study included a hyperglobulinemia in 13/37 (35%), neutrophilia in 11/37 (30%), and a monocytosis in 3/37 (8%) of dogs, which is similar to findings in other studies of dogs with *Coccidioides* encephalitis though less frequently observed compared to dogs with respiratory and musculoskeletal manifestations of the disease.[4,7,13]

There is an increased incidence of coccidioidomycosis in young (<5-6 years), large-breed (>20 kg) dogs.[3,13] Two-thirds (30/45) of dogs in the present study weighed >20 kg, with 14 of these 30 dogs weighing >30 kg. Of note, 15/45 dogs (33%) in the current study were > 7 years of age, with 7/45 dogs between 10 and 13 years old and only 9/45 dogs between 1.5 and 3 years old. This highlights the need to include coccidioidomycosis as a differential in older dogs presenting with acute onset intracranial signs, particularly in areas where *Coccidioides* is endemic or in dogs with a travel history to endemic regions.

Dogs in the current study were treated with fluconazole at a median dose of 9.4 mg/kg PO q12h. In the region surrounding the authors' institution, a fluconazole dose of 10 mg/kg q12h up to a maximum of 400 mg/day is recommended for treatment of disseminated coccidioidomycosis in dogs.[11,15] To the authors' knowledge, there have been no studies evaluating the efficacy of this dose compared to the standard dosage of 5 mg/kg q12h. Given the long duration of treatment required and risk for hepatotoxicosis, there is a need to determine the optimal dose of fluconazole for successful treatment of *Coccidioides* meningoencephalitis. This could involve comparison of serum and CSF fluconazole levels in dogs receiving the 10 mg/kg dose versus the published 5 mg/kg dose, as has been similarly investigated in human patients with HIV-associated *Cryptococcus* meningitis.[24] Likewise, the optimal duration of antifungal treatment for dogs with CNS coccidioidomycosis remains unknown. The usual practice is to continue treatment for a minimum of 1-year after diagnosis.[5,15] However, as in human patients with *Coccidioides* meningitis, azole therapy is often continued for longer because of the risk for relapse of disseminated disease after discontinuation of drug administration.[6,15,18,23,25] A finding of this study was the number of dogs that were receiving appropriate doses of compounded fluconazole at the time of the onset of neurological signs. In 7 dogs receiving compounded fluconazole at the time of MRI, transitioning to a generic formulation at essentially the same prescribed dose resulted in improvement in neurologic status. It has been suggested that compounded antifungal

medications might not provide adequate serum concentrations compared to generic formulations.[26] Although it has been established that itraconazole does not maintain stability when compounded, this has not been thoroughly evaluated for fluconazole.[2,15] A previous analysis of compounded formulations from 4 different pharmacies in the United States found the dose of fluconazole to be unreliable.[26] The positive response to therapy after a change from compounded to generic fluconazole in this study sample suggests that compounded formulations of fluconazole might be less reliable and could increase the risk for treatment failure in cases of CNS coccidioidomycosis.

Previous publications have stated that the prognosis for CNS coccidioidomycosis is generally poor.[2,5] Results of this study, however, suggest a more favorable prognosis with appropriate medical treatment. Excluding the 6 dogs lost to follow-up <12-months after diagnosis as well as the 5 dogs clinically doing well but had yet to be followed for >1-year, 82% (28/34) of dogs diagnosed with intracranial *Coccidioides* infection were alive and clinically well at follow-up ≥1-year after imaging diagnosis.

Factors which might be associated with a less favorable prognosis include evidence of ventriculitis and combined therapy with fluconazole and long-term phenobarbital and carprofen. Two dogs in the current study had MRI changes consistent with ventriculitis. Both dogs had an initially favorable response to treatment followed by a rapid neurologic decline several months later. Repeat imaging was performed for 1 of these dogs and revealed the development of an obstructive hydrocephalus. Ventriculitis has been well-documented in cases of canine CNS blastomycosis and is associated with obstructive hydrocephalus and rapid neurologic deterioration in those dogs.[27,28] Individual case reports also exist describing a ventriculitis in dogs and cats with cryptococcal meningitis.[27] Although ventriculitis is a well-known phenomenon in people with intracranial *Coccidioides* infection, we were unable to find reports of *Coccidioides*-induced ventriculitis in dogs at the time of writing. Surgical intervention in the form of ventriculoperitoneal shunting could help to improve outcome for the minority of dogs whom develop secondary obstructive hydrocephalus, as has been previously suggested for blastomycosis in dogs, although these dogs do typically require long-term antifungal and corticosteroid treatment.[28]

One dog in the present study was euthanized 1-month after MRI because of severe hepatobiliary complications presumed secondary to prior treatment with carprofen, phenobarbital, and fluconazole. This dog's serum phenobarbital concentration on presentation was >60 μg/mL, consistent with toxicosis. Coadministration of fluconazole, a hepatic microsomal cytochrome-P450 enzyme inhibitor, can reduce phenobarbital metabolism, leading to increased serum concentration and resultant toxicosis.[29] Therefore, concurrent use of fluconazole and phenobarbital must be done cautiously, for a limited period of time, and involve frequent monitoring of serum activity of liver-derived enzymes and liver function. Furthermore, concurrent use of carprofen with fluconazole can increase serum concentration of fluconazole, thereby exacerbating potential adverse effects from this medication triad. For these cases which require long-term therapy with azole antifungal medication, the authors recommend using anticonvulsants that do not undergo hepatic metabolism.

Surgical resection could potentially be advantageous compared to medical therapy alone.[7,27] Surgery offers the benefit of definitive diagnosis and might be appropriate in cases of seronegative disease or in which the imaging appearance is atypical or lesion extra-axial, but surgery also incurs added costs and potential morbidity and does not eliminate the need for long-term antifungal therapy.[7,15] Lesions are often intraparenchymal and as such are not easily accessible surgically. Furthermore, the favorable clinical response to medical treatment alone in most cases outweighs the need for surgical resection. Repeat MRI has the ability to demonstrate resolution in response to therapy, thereby providing a lower cost and less invasive option for antemortem confirmation of the presumptive diagnosis. Additionally, more pet owners might be likely to pursue this option when compared to the alternative of surgical resection or brain biopsy for histopathology.

Limitations of this study arise primarily from its retrospective nature. MRI sequences for diagnosis and treatment protocols were not standardized; additional infectious disease testing was not performed in all cases because of owner financial limitations and high clinical suspicion for coccidioidomycosis. Three dogs were seropositive for *E. canis*, 2 of which had a history of ehrlichiosis and treatment years prior with persistently positive IgG titers; *E. canis* PCR on the date of MRI was negative in 1 of these dogs. The third dog with positive *E. canis* serology had a low titer and responded well to treatment for coccidioidomycosis alone, with complete lesion resolution on MRI 84-months after diagnosis. To the authors' knowledge, *E. canis* has not been reported to cause MRI abnormalities like those seen in the study sample. No other infections are common in this region, and none of the dogs had a history of travel to regions where other fungal infections are common. Histopathologic confirmation of the diagnosis would have been ideal in all dogs, but because of the generally favorable response to medical treatment, surgical biopsy was not pursued. Unfortunately, necropsy also was not permitted for those dogs that died during the study period. Additionally, repeat MRI was not performed in all cases to confirm the presumptive diagnosis. Nevertheless, the authors propose that the documentation of a positive serum titer which declined during therapy, favorable clinical response to treatment, and duration of follow-up allows for exclusion of other possible etiologies, such as immune-mediated meningoencephalitis or neoplasia, which would be expected to fail treatment over time. CSF analysis was performed in only 4/45 dogs. The decision to not obtain CSF was often made because of perceived increased risk as a result of MRI evidence of extensive edema creating a midline shift or other mass effect with or without concurrent herniation. Given the consistent imaging characteristics of both forms of intraparenchymal *Coccidioides* infection in the brain of dogs and utility of repeat MRI, a lack of supportive CSF findings should not preclude the diagnosis.

In summary, there are characteristic MRI findings that can suggest the presence of intracranial *Coccidioides* infection in dogs, particularly when combined with clinical data and serologic testing. An increased awareness of the clinical presentation and MRI features of this disease will allow for more prompt diagnosis and treatment. Overall, the authors propose that the prognosis for intracranial coccidioidomycosis in dogs is more favorable with targeted medical treatment than previously reported.

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