Magnetic resonance imaging of intracranial inflammatory conditions in dogs: sensitivity of subtraction images versus pre- and post-gadolinium T1-weighted image pairs

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Running head: MR imaging of intracranial inflammation

Abstract

Ante mortem diagnosis of canine meningoencephalitis is usually based on the results of neurologic examination, cerebrospinal fluid analysis, and magnetic resonance (MR) imaging. It has been hypothesized that subtraction MR imaging may increase the sensitivity of MR for intracranial inflammatory lesions compared to conventional post-gadolinium T1-weighted imaging. Sensitivity of pre- and post-gadolinium (C-/C+) image pairs and dynamic subtraction (DS) images was compared in a retrospective diagnostic accuracy study of 52 dogs with inflammatory cerebrospinal fluid and 67 dogs with idiopathic epilepsy. Series of transverse C-/C+ and DS images were reviewed independently for signs of abnormal enhancement affecting the pachymeninges, leptomeninges or intra-axial structures. Sensitivity of C-/C+ image pairs and DS images was 48% (95% CI 35-61%) and 65% (95% CI 52-77%), respectively (p=0.01). Intra-axial lesions were observed more frequently than meningeal lesions in both C-/C+ (43% versus 31%) and DS images (61% versus 22%). The difference in sensitivities of C-/C+ and DS series was entirely due to increased sensitivity of DS images for intra-axial lesions. Eight (12%) dogs with epilepsy had evidence of intra-axial gadolinium accumulation affecting the cerebral cortex in DS images. This finding may represent a false positive result or a true sign of pathology, possibly associated with a leaky blood-brain barrier in areas of the brain affected by neovascularization secondary to repeated seizures. Results suggest that DS imaging has higher sensitivity than comparison of pre- and post-gadolinium image pairs for inflammatory intra-axial lesions.

Introduction

Intracranial inflammatory conditions in dogs include a range of idiopathic, immune-mediated and infectious meningoencephalitides.[1-5] Signs of intracranial inflammation are detected inconsistently in magnetic resonance (MR) images of dogs, and sensitivity of MR is considered to be only moderate.[6-9] Cerebrospinal fluid evaluation is considered to be a more sensitive test for intracranial inflammation than MR. For example, in a study of 188 dogs with inflammatory brain conditions, 88% had abnormal cerebrospinal fluid with elevations in white cell counts and/or total protein.[10] Hence the main aims of MR in dogs with clinical signs suggestive of intracranial inflammation are to distinguish inflammatory lesions from other types of pathology that could produce similar clinical signs, such as neoplasia, and to identify signs of increased intracranial pressure, which would contraindicate collection of cerebrospinal fluid from the cerebellomedullary cistern. [11,12]

In dogs with intracranial inflammatory conditions, infiltration of the meninges by inflammatory cells is liable to occur, hence the meninges are a target for MR, although the extent and type of infiltration is variable and MR findings are inconsistent.[6-9] T1-weighted post-gadolinium imaging is frequently used to examine the meninges.[13-15] Normal meningeal enhancement is more conspicuous in MR images obtained using a dynamic subtraction technique than in native post-gadolinium T1-weighted images[16], and in studies of humans with intracranial conditions, sensitivity of observers for detecting enhancement in MR images was higher when using subtraction images than when making a comparison of a parallel (side by side) pre- and post-gadolinium image pair.[17] Hence, it has been suggested that dynamic subtraction MR imaging

should be considered for use in dogs because of the possibility of increased sensitivity for lesions affecting the meninges, such as may occur in inflammatory conditions.[16]

The aim of the present study was to test the hypothesis that there is a difference in sensitivity between pre- and post-gadolinium T1-weighted image pairs (C-/C+) and dynamic subtraction (DS) images for intracranial inflammatory disease in dogs.

Materials and methods

A retrospective diagnostic accuracy study was done by searching medical records of the Queen Mother Hospital for Animals between December 2012 (when use of dynamic subtraction MR studies began) and November 2015 for dogs that had MR imaging and cerebrospinal fluid analysis or histology results compatible with intracranial inflammation. Inclusion criteria were dogs that had C-/C+ and DS series of the brain, cerebrospinal fluid analysis performed under the same anesthetic with raised total protein (>0.25g/L) and raised white cell count (>5/mm^3), and/or altered white cell distribution and cytology findings consistent with inflammation, and/or histology performed following surgery or necropsy within 5 days of MR imaging. In dogs that satisfied the inclusion criteria, age, gender, neuter status, weight, breed, clinical signs, neurological examination findings, and clinical diagnosis were recorded. A group for comparison was created by searching for dogs that had MR imaging of the brain during the same period and a subsequent clinical diagnosis of idiopathic epilepsy based on signalment, history of recurrent seizures, lack of interictal neurologic signs, and cerebrospinal fluid analysis within normal limits.

MR imaging using a standardized protocol was performed in all dogs under general anesthesia in a 1.5 T magnet using a flexible surface coil (Intera Pulsar System, Philips Medical Systems, Reigate, UK). Spin–echo T1-weighted (TR 570 ms, TE 15 ms) pre- and post-gadolinium transverse images were acquired with image slice thickness 3.5mm and interslice gap 1 mm. Field of view was adjusted individually; typical values for a medium-sized dog were 120 × 120 mm with a 224 × 224 image matrix, hence pixel size was approximately 0.5 × 0.5 mm. Subtraction of pre- from post-gadolinium T1-weighted images was performed using a dynamic study sequence comprising two T1-weighted image series separated by an interval during which the sequence was paused, an IV bolus of 0.1 mmol/kg gadobuterol (Gadovist 1.0 mmol/ml, Bayer plc, Newbury, UK) was administered, and the sequence restarted within 1 min.[16] This acquisition produced both C-/C+ image pairs and DS images.

MR images were reviewed independently by a board-certified radiologist (CRL) without knowledge of any clinical information. C-/C+ image pairs were viewed together, side-by-side, in order to describe the pattern of enhancement. Series of C-/C+ images were reviewed in case number order; DS images were reviewed in reverse chronologic order several days later. None of the other image series that were acquired for these dogs were reviewed for this study. C-/C+ and DS images were reviewed for signs of abnormal enhancement affecting the pachymeninges, leptomeninges or intra-axial structures, and abnormalities were classified as focal (localized at one place), multifocal (localized at multiple places), or diffuse (not localized, spread out). Imaging signs considered compatible with pachymeningeal lesions were an abnormal signal forming a smooth or nodular curve parallel to the inner table of the skull in multiple contiguous images and/or a dural tail sign. Signs considered compatible with

leptomeningeal lesions were an abnormal signal forming a smooth or nodular curve occupying the sulcal and/or gyral subarachnoid spaces in multiple contiguous images. Each series of images was given a diagnosis score as follows: 1, definitely normal; 2, probably normal; 3, equivocal; 4, probably abnormal; 5, definitely abnormal (Table 1). Series graded 4 or 5 were considered positive for inflammatory disease. Sensitivities of C-/C+ and DS images were calculated as the number of positive results divided by the number of dogs with intracranial inflammation.

Significance of differences in median age and body weight of dogs with intracranial inflammation and dogs in the comparison group was tested using the Mann-Whitney test. The difference in sensitivity between C-/C+ and DS images was tested using McNemar's test.[18] Testing was done by CRL using a computational website (http://vassarstats.net).

Results

Records were found of 52 dogs with intracranial inflammation that satisfied the inclusion criteria. No dogs were excluded. There were 25 males (16 neutered) and 27 females (15 neutered). Their median (range) age at the time of MR imaging was 4.1 years (10 months-12.5 years) and median (range) body weight was 8.5kg (1.6-55kg). Breeds were West Highland White terrier (n=7), mixed breed (7), French Bulldog (6), Maltese terrier (4), Shih Tzu (4), Pug (3), Chihuahua (2), Jack Russell terrier (2), Lhasa Apso (2), Labrador Retriever (2) and one of each of thirteen other breeds (Bernese Mountain dog, German Wirehaired Pointer, Whippet, Toy Poodle, Miniature Schnauzer, Shetland sheepdog, Finnish Lapphund, Bull terrier, English

Springer spaniel, Welsh terrier, Italian Spinone, Yorkshire Terrier and Griffon Bruxellois).

For the intracranial inflammation group, diagnosis in 29 (56%) dogs was based on white cell count and total protein above normal limits and abnormal cytology findings. In these dogs, median (range) white cell count was 88/mm^3 (6-1065/mm^3) and total protein was 0.5g/L (0.26-1.96 g/L). In 13 (25%) dogs, the diagnosis was based on abnormal cerebrospinal fluid cytology and normal or abnormal white cell count in the presence of normal cerebrospinal fluid protein level. In these dogs, median (range) white cell count was 9/mm^3 (0-480/mm^3) and total protein was 0.19g/L (0.07-0.23 g/L). Diagnosis in the remaining 10 (19%) dogs was based on histologic findings. Diagnoses were granulomatous meningoencephalomyelitis in 6 dogs, necrotizing meningoencephalitis in 2 dogs, neosporosis, and non-specific meningitis (Table 2).

The comparison group comprised 67 dogs. There were 48 males (36 neutered) and 19 females (14 neutered). Their median (range) age was 3.3 years (3 months-9.4 years) and median (range) body weight was 20.6kg (2-53kg). There was no significant difference in age (p=0.2), but dogs in the comparison group had greater median body weight than dogs with intracranial inflammation (p=0.001). Breeds of dogs in the comparison group were mixed breed (n=13), Labrador retriever (6), Chihuahua (4), Siberian Husky (3), Hungarian Vizsla (3), Pug (3), German Shepherd dog (3), Leonberger (2), Dogue de Bordeaux (2), Maltese terrier (2), Staffordshire Bull terrier (2), Bichon Frise (2), Cocker Spaniel (2), French Bulldog (2), Miniature Schnauzer (2), English Springer Spaniel (2), Mastiff (2) and one of each of twelve other breeds (Cavalier King Charles Spaniel, Dachshund, Beagle, Lakeland terrier, Border Collie, Shih Tzu, Jack Russell terrier, Dobermann, Petit Basset Griffon Vendeen, Lowchen, Lurcher and Spanish water dog). In

the comparison group, median (range) white cell count was 1/mm^3 (0-5/mm^3) and total protein was 0.15g/L (0-0.25 g/L). Cytology found no significant signs of inflammation in any of these dogs.

Results of MR imaging are summarized in table 3. Sensitivity of C-/C+ image pairs and DS images was 25/52 (48%, 95% CI 35-61%) and 34/52 (65%, 95% CI 52-77%), respectively (p=0.01). Intra-axial lesions were observed more frequently than meningeal lesions in both C-/C+ (43% versus 31%) and DS images (61% versus 22%). The difference in sensitivities of C-/C+ and DS series was entirely due to increased sensitivity of DS images for intra-axial lesions (Table 4) (Figures 1 and 2).

No dogs in the comparison group were interpreted as abnormal on the basis of C-/C+ image pairs, but 8/67 (12%) had gadolinium accumulation interpreted as probably abnormal (Table 3). In these dogs, gadolinium accumulation was described as affecting the superficial cerebral cortex in 4 and hippocampus in 4 (Figure 3). Evidence of ependymal gadolinium accumulation was noted in one of the dogs with cortical enhancement and one of the dogs with hippocampal enhancement. No significant differences in age, weight or time between last seizure and MR imaging were identified between the 8 dogs with abnormal gadolinium accumulation and the remaining dogs.

Discussion

This study supports the conclusions of previous studies that found sensitivity of MR imaging for

intracranial inflammatory conditions to be no better than moderate.[3,4,8,9,11,13,15] This study found evidence of significantly higher sensitivity of DS images for inflammatory lesions compared to C-/C+ image pairs. This difference reflects increased sensitivity of DS images for intra-axial lesions rather than for meningeal lesions. On the basis of a previous study of dogs with meninges presumed to be normal[16], we hypothesized that DS images would have increased sensitivity for meningeal lesions, but have found no support for that hypothesis. Despite meningitis being a frequent histologic finding in dogs with inflammatory brain conditions, meningeal changes are infrequently detected by MR[3,5-9], and DS imaging does not appear to affect this.

In the present study, MR signs of intra-axial lesions were identified more frequently than meningeal lesions in dogs with intracranial inflammatory conditions. A study of 18 dogs with inflammatory brain disease found that 93% had intra-axial lesions, 87% had contrast enhancement, and 59% had meningeal enhancement.[11] In another study of 11 dogs with inflammatory brain disease, intra-axial lesions were characterized by influx of inflammatory cells, necrosis and cavitation, vascular leakage and proliferation, and dilated vessels.[19] A small majority of dogs (6/11, 55%) in that study had heterogeneous contrast accumulation in intra-axial lesions, but the remainder showed no contrast enhancement.[19] Subtraction was used in that study to increase the conspicuity of contrast enhancement, but the results of native and subtraction images were not compared.

The finding of possible intra-axial gadolinium accumulation in the brain of 12% dogs with epilepsy was unexpected. These dogs were selected for the comparison group on the

assumption that they would have no MR abnormalities, and that their inclusion would help reduce observer bias. It is unclear if this result represents a classification error, in which some dogs with inflammatory conditions had normal cerebrospinal fluid, a false positive occurring because the observer tended to overinterpret DS images, or a true sign of pathology, possibly associated with a leaky blood-brain barrier in areas of the brain affected by neovascularization secondary to repeated seizures. Reversible MR abnormalities, evident on T2-weighted and T1-weighted images, have been reported in dogs up to 14 days following seizure activity, and in one dog involving contrast enhancement of both piriform and temporal lobes.[20] cerebrospinal fluid analysis of this dog found an elevated total protein but normal white cell count. Lesions were no longer evident at a repeat MR study 11 weeks later, and the cerebrospinal fluid was within normal limits, the dog having had no seizures in the intervening period.[20] Another study of 11 Finnish Spitz dogs with focal epilepsy found post-contrast enhancement of the right parietal cortex in one dog, which was not visible on repeat MR imaging 13 months later.[21] The time between last seizure activity and MR imaging was not detailed, but this dog was the only one in the group to suffer from primary generalized seizures. Histopathology was not performed in those cases and cannot be related to the MR findings. Other animal and human studies have found evidence of blood-brain barrier damage in areas of the brain affected by neovascularization secondary to repeated seizures in epileptic individuals.[22] Blood-brain barrier damage may persist in the chronic epileptic phase, act as a factor potentiating seizures, and is a potential target for drug therapy, particularly in patients whose seizures are not controlled by current anti-epileptic drugs.[22,23] A study of Shetland Sheepdogs with familial epilepsy found signs of angiogenesis and microglial activation were associated with seizure-induced neuronal

death in the cerebral cortex.[24] It is thought that neovascularization and associated inflammation may accelerate seizure-induced neuronal death in dogs with epilepsy.[24] The subtle signs of post-contrast enhancement observed in DS images in the present study could represent foci of blood-brain barrier damage that is not detectable with standard C-/C+ image pairs. Unfortunately, histopathology to better define the nature of possible lesions, and to rule out other causes of contrast accumulation, such as inflammatory lesions, was not possible because seizures in these dogs were managed satisfactorily. Similarly, another limitation of the present study is that diagnosis of inflammatory intracranial disease was mainly based on results of cerebrospinal fluid analysis, with relatively few dogs undergoing necropsy and histopathologic examination of the brain. The disadvantages associated with lack of histologic diagnosis must be balanced with the advantages of including a representative sample of cases, including those in which the clinical signs may be relatively mild and well controlled with medication.[6]

In summary, this study found evidence of significantly higher sensitivity of DS images for the detection of intra-axial inflammatory lesions compared to C-/C+ image pairs. The unexpected finding of possible intra-axial gadolinium accumulation in the brain of dogs with epilepsy could be associated with blood-brain barrier damage in areas of the brain affected by repeated seizures. The possibility that dynamic subtraction MR imaging may have an application in the clinical assessment of dogs with idiopathic epilepsy merits further investigation.

List of Author Contributions

Category 1

(a) Conception and Design

Helen Dirrig & Christopher R. Lamb

(b) Acquisition of Data

Helen Dirrig & Christopher R. Lamb

(c) Analysis and Interpretation of Data

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Category 2

(a) Drafting the Article

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Category 3

(a) Final Approval of the Completed Article

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Table 1. Definitions of diagnosis scores

1. Definitely normal:	Narrow, uniform, slight meningeal enhancement; no intra-axial enhancement evident
2. Probably normal:	Narrow, uniform, moderate meningeal enhancement; no intra-axial enhancement evident
3. Equivocal:	Unable to conclude probably normal or probably abnormal
4. Probably abnormal:	Meningeal enhancement more intense and/or non-uniform and/or thicker than considered normal and/or subtle evidence of intra-axial enhancement
5. Definitely abnormal:	Markedly hyperintense and/or thickened meninges and/or axial displacement of neural tissue and/or moderate or marked intra-axial enhancement

Table 2. Diagnoses and cerebrospinal fluid cytology results for 52 dogs with inflammatory intracranial conditions

Method of diagnosis	Diagnosis	Cerebrospinal fluid cytology	n
Histology	GME	Mononuclear pleocytosis	2
	GME	Neutrophilic pleocytosis	2
	GME	NP	2
	NME	NP	2
	Neosporosis	Neutrophilic pleocytosis	1
	Non-specific meningitis	NP	1
Cerebrospinal fluid	MUE	Mononuclear pleocytosis	17
		Mixed pleocytosis	14
		Lymphocytic pleocytosis	9
		Neutrophilic pleocytosis	1
		Eosinophilic pleocytosis	1

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GME, Granulomatous meningoencephalomyelitis; NME, Necrotizing meningoencephalitis; MUE, Meningoencephalitis of unknown etiology;

NP, Not performed;

Table 3. Results of MR imaging

	Intracranial inflammation group n=52					Control group n=67				
MR sequence	Diagnosis score					Diagnosis score				
	1	2	3	4	5	1	2	3	4	5
C-/C+	15 (29%)	9 (17%)	3 (6%)	7 (13%)	18 (35%)	54 (81%)	12 (18%)	1 (1%)	0 (0%)	0 (0%)
DS	8 (15%)	6 (12%)	4 (8%)	10 (19%)	24 (46%)	34(51%)	17 (25%)	8 (12%)	8 (12%)	0 (0%)

Values are number and percent dogs with diagnosis scores, where 1, definitely normal; 2, probably normal; 3, equivocal; 4, probably abnormal; 5, definitely abnormal.

C-/C+, Pre- and post-gadolinium T1-weighted image pairs; DS, Dynamic subtraction images

Table 4. Distribution of MR lesions in 52 dogs with inflammatory intracranial conditions

	Pachymeningeal lesions			Leptomeningeal lesions			Intra-axial lesions		
MR sequence	F	M	D	F	M	D	F	M	D
C-/C+	2 (4%)	0 (0%)	2 (4%)	4 (8%)	0 (0%)	8 (15%)	9(17%)	13 (25%)	1 (1%)
DS	0 (0%)	0 (0%)	1 (1%)	3(6%)	0 (0%)	8 (15%)	12(23%)	19 (37%)	1 (1%)

Values are number and percent dogs with diagnosis score 4 or 5 and suspected focal (F), multifocal (M) or diffuse (D) lesions.

C-/C+, Pre- and post-gadolinium T1-weighted image pairs; DS, Dynamic subtraction images

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Legends

Figure 1. Similar results for C-/C+ image pair and DS images in a dog with inflammatory cerebrospinal fluid and histologic diagnosis of necrotizing meningoencephalitis. A) T1-weighted image, B) post-gadolinium T1-weighted image, C) corresponding DS image. There is diffuse slight hypointensity affecting cortical grey matter to the right of midline in the T1-weighted image and moderate enhancement of the cerebral cortex and leptomeninges in the post-gadolinium T1-weighted image and DS image.

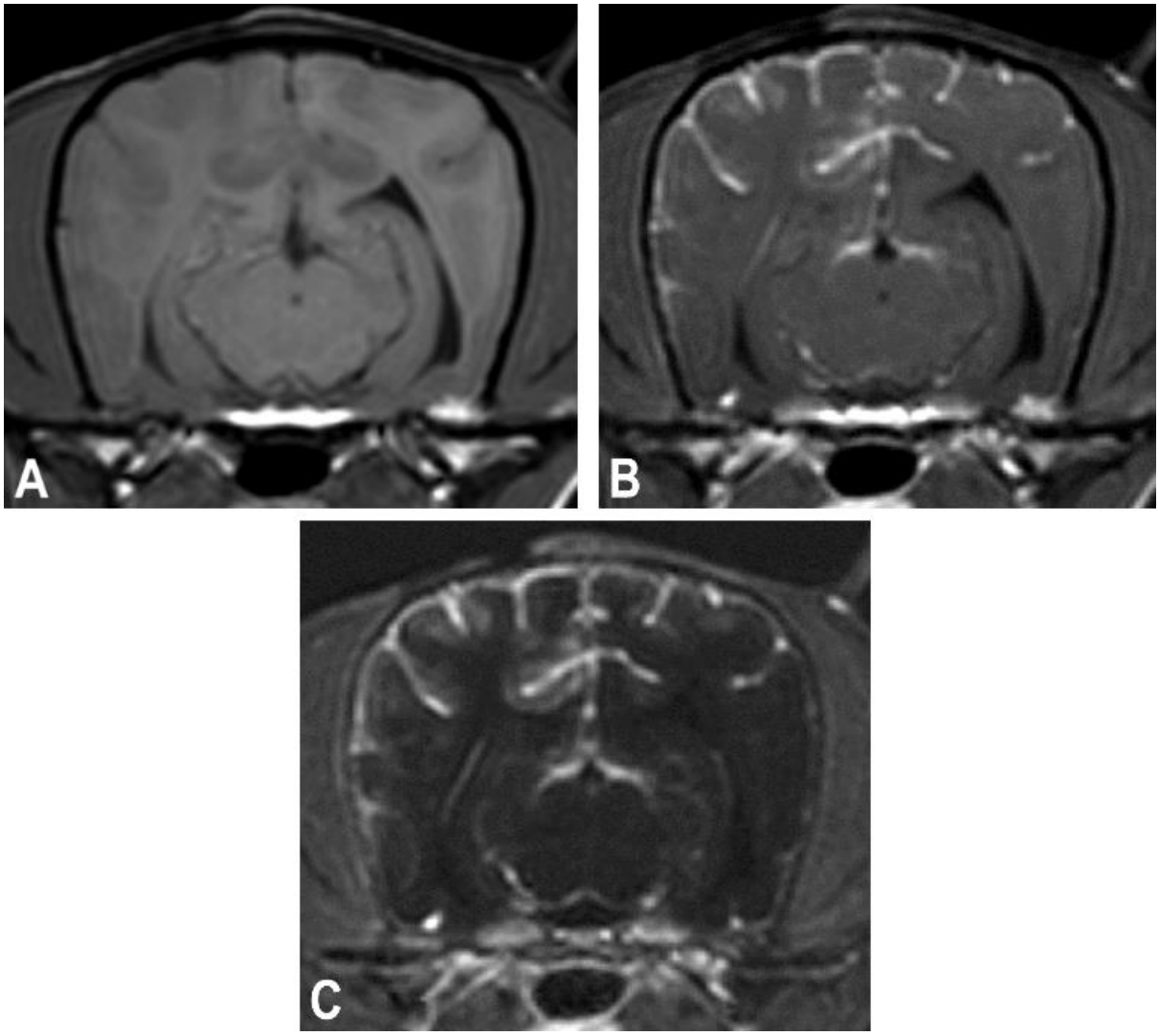

Figure 2. Different results for C-/C+ image pair and DS images in a dog with inflammatory cerebrospinal fluid and histologic diagnosis of granulomatous meningoencephalomyelitis. A) T1-weighted image, B) post-gadolinium T1-weighted image, C) corresponding DS image. There is focal moderate enhancement of the right piriform lobe in the DS image that was not recognized during review of the C-/C+ image pair.

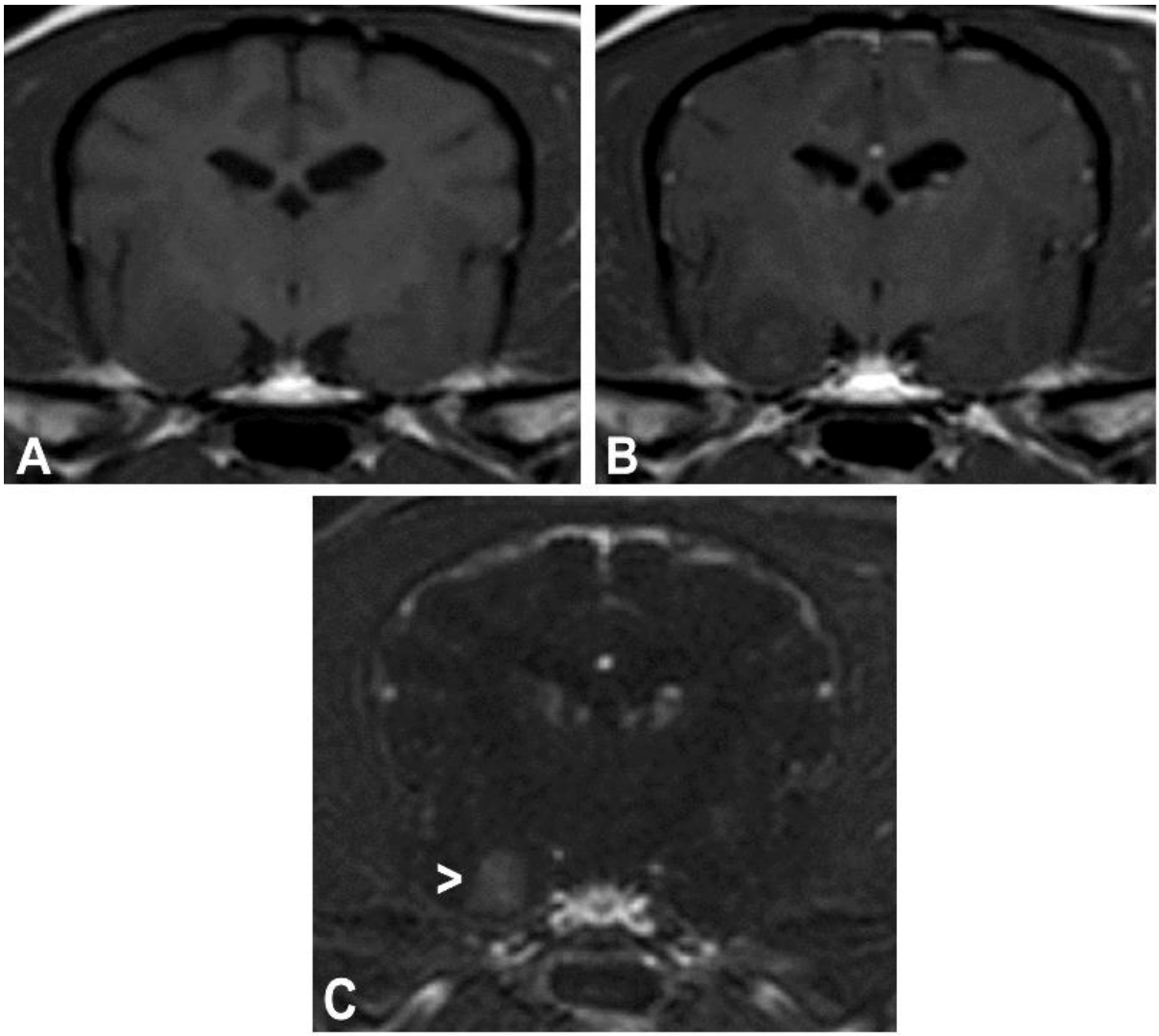

Figure 3. Examples of DS images interpreted as showing abnormal gadolinium uptake in dogs with clinical diagnosis of idiopathic epilepsy. A) Multifocal cortical enhancement (arrowheads), B) bilateral hippocampal enhancement (arrowheads), C) ependymal enhancement (arrowhead).