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TITLE: 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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1 **Magnetic resonance imaging of intracranial inflammatory conditions in dogs: sensitivity of**

2 **subtraction images versus pre- and post-gadolinium T1-weighted image pairs**

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12

13   **Abstract**

14   Ante mortem diagnosis of canine meningoencephalitis is usually based on the results of

15   neurologic examination, cerebrospinal fluid analysis, and magnetic resonance (MR) imaging. It

16   has been hypothesized that subtraction MR imaging may increase the sensitivity of MR for

17   intracranial inflammatory lesions compared to conventional post-gadolinium T1-weighted

18   imaging. Sensitivity of pre- and post-gadolinium (C-/C+) image pairs and dynamic subtraction

19   (DS) images was compared in a retrospective diagnostic accuracy study of 52 dogs with

20   inflammatory cerebrospinal fluid and 67 dogs with idiopathic epilepsy. Series of transverse C-

21   /C+ and DS images were reviewed independently for signs of abnormal enhancement affecting

22   the pachymeninges, leptomeninges or intra-axial structures. Sensitivity of C-/C+ image pairs

23   and DS images was 48% (95% CI 35-61%) and 65% (95% CI 52-77%), respectively (p=0.01). Intra-

24   axial lesions were observed more frequently than meningeal lesions in both C-/C+ (43% versus

25   31%) and DS images (61% versus 22%). The difference in sensitivities of C-/C+ and DS series was

26   entirely due to increased sensitivity of DS images for intra-axial lesions. Eight (12%) dogs with

27   epilepsy had evidence of intra-axial gadolinium accumulation affecting the cerebral cortex in DS

28   images. This finding may represent a false positive result or a true sign of pathology, possibly

29   associated with a leaky blood-brain barrier in areas of the brain affected by neovascularization

30   secondary to repeated seizures. Results suggest that DS imaging has higher sensitivity than

31   comparison of pre- and post-gadolinium image pairs for inflammatory intra-axial lesions.

32

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

54   should be considered for use in dogs because of the possibility of increased sensitivity for

55   lesions affecting the meninges, such as may occur in inflammatory conditions.[16]

56   The aim of the present study was to test the hypothesis that there is a difference in sensitivity

57   between pre- and post-gadolinium T1-weighted image pairs (C-/C+) and dynamic subtraction

58   (DS) images for intracranial inflammatory disease in dogs.

59

60   **Materials and methods**

61   A retrospective diagnostic accuracy study was done by searching medical records of the Queen

62   Mother Hospital for Animals between December 2012 (when use of dynamic subtraction MR

63   studies began) and November 2015 for dogs that had MR imaging and cerebrospinal fluid

64   analysis or histology results compatible with intracranial inflammation. Inclusion criteria were

65   dogs that had C-/C+ and DS series of the brain, cerebrospinal fluid analysis performed under the

66   same anesthetic with raised total protein (>0.25g/L) and raised white cell count (>5/mm^3),

67   and/or altered white cell distribution and cytology findings consistent with inflammation,

68   and/or histology performed following surgery or necropsy within 5 days of MR imaging. In dogs

69   that satisfied the inclusion criteria, age, gender, neuter status, weight, breed, clinical signs,

70   neurological examination findings, and clinical diagnosis were recorded. A group for

71   comparison was created by searching for dogs that had MR imaging of the brain during the

72   same period and a subsequent clinical diagnosis of idiopathic epilepsy based on signalment,

73   history of recurrent seizures, lack of interictal neurologic signs, and cerebrospinal fluid analysis

74   within normal limits.

75 MR imaging using a standardized protocol was performed in all dogs under general anesthesia

76 in a 1.5 T magnet using a flexible surface coil (Intera Pulsar System, Philips Medical Systems,

77 Reigate, UK). Spin–echo T1-weighted (TR 570 ms, TE 15 ms) pre- and post-gadolinium

78 transverse images were acquired with image slice thickness 3.5mm and interslice gap 1 mm.

79 Field of view was adjusted individually; typical values for a medium-sized dog were 120 × 120

80 mm with a 224 × 224 image matrix, hence pixel size was approximately 0.5 × 0.5 mm.

81 Subtraction of pre- from post-gadolinium T1-weighted images was performed using a dynamic

82 study sequence comprising two T1-weighted image series separated by an interval during which

83 the sequence was paused, an IV bolus of 0.1 mmol/kg gadobuterol (Gadovist 1.0 mmol/ml,

84 Bayer plc, Newbury, UK) was administered, and the sequence restarted within 1 min.[16] This

85 acquisition produced both C-/C+ image pairs and DS images.

86 MR images were reviewed independently by a board-certified radiologist (CRL) without

87 knowledge of any clinical information. C-/C+ image pairs were viewed together, side-by-side, in

88 order to describe the pattern of enhancement. Series of C-/C+ images were reviewed in case

89 number order; DS images were reviewed in reverse chronologic order several days later. None

90 of the other image series that were acquired for these dogs were reviewed for this study. C-/C+

91 and DS images were reviewed for signs of abnormal enhancement affecting the

92 pachymeninges, leptomeninges or intra-axial structures, and abnormalities were classified as

93 focal (localized at one place), multifocal (localized at multiple places), or diffuse (not localized,

94 spread out). Imaging signs considered compatible with pachymeningeal lesions were an

95 abnormal signal forming a smooth or nodular curve parallel to the inner table of the skull in

96 multiple contiguous images and/or a dural tail sign. Signs considered compatible with

97   leptomeningeal lesions were an abnormal signal forming a smooth or nodular curve occupying

98   the sulcal and/or gyral subarachnoid spaces in multiple contiguous images. Each series of

99   images was given a diagnosis score as follows: 1, definitely normal; 2, probably normal; 3,

100   equivocal; 4, probably abnormal; 5, definitely abnormal (Table 1). Series graded 4 or 5 were

101   considered positive for inflammatory disease. Sensitivities of C-/C+ and DS images were

102   calculated as the number of positive results divided by the number of dogs with intracranial

103   inflammation.

104   Significance of differences in median age and body weight of dogs with intracranial

105   inflammation and dogs in the comparison group was tested using the Mann-Whitney test. The

106   difference in sensitivity between C-/C+ and DS images was tested using McNemar's test.[18]

107   Testing was done by CRL using a computational website (http://vassarstats.net).

108

109   **Results**

110   Records were found of 52 dogs with intracranial inflammation that satisfied the inclusion

111   criteria. No dogs were excluded. There were 25 males (16 neutered) and 27 females (15

112   neutered). Their median (range) age at the time of MR imaging was 4.1 years (10 months-12.5

113   years) and median (range) body weight was 8.5kg (1.6-55kg). Breeds were West Highland White

114   terrier (n=7), mixed breed (7), French Bulldog (6), Maltese terrier (4), Shih Tzu (4), Pug (3),

115   Chihuahua (2), Jack Russell terrier (2), Lhasa Apso (2), Labrador Retriever (2) and one of each of

116   thirteen other breeds (Bernese Mountain dog, German Wirehaired Pointer, Whippet, Toy

117   Poodle, Miniature Schnauzer, Shetland sheepdog, Finnish Lapphund, Bull terrier, English

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

119   For the intracranial inflammation group, diagnosis in 29 (56%) dogs was based on white cell

120   count and total protein above normal limits and abnormal cytology findings. In these dogs,

121   median (range) white cell count was 88/mm^3 (6-1065/mm^3) and total protein was 0.5g/L (0.26-

122   1.96 g/L). In 13 (25%) dogs, the diagnosis was based on abnormal cerebrospinal fluid cytology

123   and normal or abnormal white cell count in the presence of normal cerebrospinal fluid protein

124   level. In these dogs, median (range) white cell count was 9/mm^3 (0-480/mm^3) and total protein

125   was 0.19g/L (0.07-0.23 g/L). Diagnosis in the remaining 10 (19%) dogs was based on histologic

126   findings. Diagnoses were granulomatous meningoencephalomyelitis in 6 dogs, necrotizing

127   meningoencephalitis in 2 dogs, neosporosis, and non-specific meningitis (Table 2).

128   The comparison group comprised 67 dogs. There were 48 males (36 neutered) and 19 females

129   (14 neutered). Their median (range) age was 3.3 years (3 months-9.4 years) and median (range)

130   body weight was 20.6kg (2-53kg). There was no significant difference in age (p=0.2), but dogs in

131   the comparison group had greater median body weight than dogs with intracranial

132   inflammation (p=0.001). Breeds of dogs in the comparison group were mixed breed (n=13),

133   Labrador retriever (6), Chihuahua (4), Siberian Husky (3), Hungarian Vizsla (3), Pug (3), German

134   Shepherd dog (3), Leonberger (2), Dogue de Bordeaux (2), Maltese terrier (2), Staffordshire Bull

135   terrier (2), Bichon Frise (2), Cocker Spaniel (2), French Bulldog (2), Miniature Schnauzer (2),

136   English Springer Spaniel (2), Mastiff (2) and one of each of twelve other breeds (Cavalier King

137   Charles Spaniel, Dachshund, Beagle, Lakeland terrier, Border Collie, Shih Tzu, Jack Russell

138   terrier, Dobermann, Petit Basset Griffon Vendeen, Lowchen, Lurcher and Spanish water dog). In

139   the comparison group, median (range) white cell count was 1/mm^3 (0-5/mm^3) and total protein

140   was 0.15g/L (0-0.25 g/L). Cytology found no significant signs of inflammation in any of these

141   dogs.

142   Results of MR imaging are summarized in table 3. Sensitivity of C-/C+ image pairs and DS

143   images was 25/52 (48%, 95% CI 35-61%) and 34/52 (65%, 95% CI 52-77%), respectively

144   (p=0.01). Intra-axial lesions were observed more frequently than meningeal lesions in both C-

145   /C+ (43% versus 31%) and DS images (61% versus 22%). The difference in sensitivities of C-/C+

146   and DS series was entirely due to increased sensitivity of DS images for intra-axial lesions (Table

147   4) (Figures 1 and 2).

148   No dogs in the comparison group were interpreted as abnormal on the basis of C-/C+ image

149   pairs, but 8/67 (12%) had gadolinium accumulation interpreted as probably abnormal (Table 3).

150   In these dogs, gadolinium accumulation was described as affecting the superficial cerebral

151   cortex in 4 and hippocampus in 4 (Figure 3). Evidence of ependymal gadolinium accumulation

152   was noted in one of the dogs with cortical enhancement and one of the dogs with hippocampal

153   enhancement. No significant differences in age, weight or time between last seizure and MR

154   imaging were identified between the 8 dogs with abnormal gadolinium accumulation and the

155   remaining dogs.

156

157   **Discussion**

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

159   intracranial inflammatory conditions to be no better than moderate.[3,4,8,9,11,13,15] This study

160   found evidence of significantly higher sensitivity of DS images for inflammatory lesions

161   compared to C-/C+ image pairs. This difference reflects increased sensitivity of DS images for

162   intra-axial lesions rather than for meningeal lesions. On the basis of a previous study of dogs

163   with meninges presumed to be normal[16], we hypothesized that DS images would have

164   increased sensitivity for meningeal lesions, but have found no support for that hypothesis.

165   Despite meningitis being a frequent histologic finding in dogs with inflammatory brain

166   conditions, meningeal changes are infrequently detected by MR[3,5-9], and DS imaging does not

167   appear to affect this.

168   In the present study, MR signs of intra-axial lesions were identified more frequently than

169   meningeal lesions in dogs with intracranial inflammatory conditions. A study of 18 dogs with

170   inflammatory brain disease found that 93% had intra-axial lesions, 87% had contrast

171   enhancement, and 59% had meningeal enhancement.[11] In another study of 11 dogs with

172   inflammatory brain disease, intra-axial lesions were characterized by influx of inflammatory

173   cells, necrosis and cavitation, vascular leakage and proliferation, and dilated vessels.[19] A small

174   majority of dogs (6/11, 55%) in that study had heterogeneous contrast accumulation in intra-

175   axial lesions, but the remainder showed no contrast enhancement.[19] Subtraction was used in

176   that study to increase the conspicuity of contrast enhancement, but the results of native and

177   subtraction images were not compared.

178   The finding of possible intra-axial gadolinium accumulation in the brain of 12% dogs with

179   epilepsy was unexpected. These dogs were selected for the comparison group on the

180   assumption that they would have no MR abnormalities, and that their inclusion would help

181   reduce observer bias. It is unclear if this result represents a classification error, in which some

182   dogs with inflammatory conditions had normal cerebrospinal fluid, a false positive occurring

183   because the observer tended to overinterpret DS images, or a true sign of pathology, possibly

184   associated with a leaky blood-brain barrier in areas of the brain affected by neovascularization

185   secondary to repeated seizures. Reversible MR abnormalities, evident on T2-weighted and T1-

186   weighted images, have been reported in dogs up to 14 days following seizure activity, and in

187   one dog involving contrast enhancement of both piriform and temporal lobes.[20] cerebrospinal

188   fluid analysis of this dog found an elevated total protein but normal white cell count. Lesions

189   were no longer evident at a repeat MR study 11 weeks later, and the cerebrospinal fluid was

190   within normal limits, the dog having had no seizures in the intervening period.[20] Another study

191   of 11 Finnish Spitz dogs with focal epilepsy found post-contrast enhancement of the right

192   parietal cortex in one dog, which was not visible on repeat MR imaging 13 months later.[21] The

193   time between last seizure activity and MR imaging was not detailed, but this dog was the only

194   one in the group to suffer from primary generalized seizures. Histopathology was not

195   performed in those cases and cannot be related to the MR findings. Other animal and human

196   studies have found evidence of blood-brain barrier damage in areas of the brain affected by

197   neovascularization secondary to repeated seizures in epileptic individuals.[22] Blood-brain barrier

198   damage may persist in the chronic epileptic phase, act as a factor potentiating seizures, and is a

199   potential target for drug therapy, particularly in patients whose seizures are not controlled by

200   current anti-epileptic drugs.[22,23] A study of Shetland Sheepdogs with familial epilepsy found

201   signs of angiogenesis and microglial activation were associated with seizure-induced neuronal

202   death in the cerebral cortex.[24] It is thought that neovascularization and associated

203   inflammation may accelerate seizure-induced neuronal death in dogs with epilepsy.[24] The

204   subtle signs of post-contrast enhancement observed in DS images in the present study could

205   represent foci of blood-brain barrier damage that is not detectable with standard C-/C+ image

206   pairs. Unfortunately, histopathology to better define the nature of possible lesions, and to rule

207   out other causes of contrast accumulation, such as inflammatory lesions, was not possible

208   because seizures in these dogs were managed satisfactorily. Similarly, another limitation of the

209   present study is that diagnosis of inflammatory intracranial disease was mainly based on results

210   of cerebrospinal fluid analysis, with relatively few dogs undergoing necropsy and

211   histopathologic examination of the brain. The disadvantages associated with lack of histologic

212   diagnosis must be balanced with the advantages of including a representative sample of cases,

213   including those in which the clinical signs may be relatively mild and well controlled with

214   medication.[6]

215   In summary, this study found evidence of significantly higher sensitivity of DS images for the

216   detection of intra-axial inflammatory lesions compared to C-/C+ image pairs. The unexpected

217   finding of possible intra-axial gadolinium accumulation in the brain of dogs with epilepsy could

218   be associated with blood-brain barrier damage in areas of the brain affected by repeated

219   seizures. The possibility that dynamic subtraction MR imaging may have an application in the

220   clinical assessment of dogs with idiopathic epilepsy merits further investigation.

221

222

223   **List of Author Contributions**

224   Category 1

225   (a) Conception and Design

226   Helen Dirrig & Christopher R. Lamb

227   (b) Acquisition of Data

228   Helen Dirrig & Christopher R. Lamb

229   (c) Analysis and Interpretation of Data

230   Helen Dirrig & Christopher R. Lamb

231   Category 2

232   (a) Drafting the Article

233   Helen Dirrig & Christopher R. Lamb

234   (b) Revising Article for Intellectual Content

235   Helen Dirrig & Christopher R. Lamb

236   Category 3

237   (a) Final Approval of the Completed Article

238   Helen Dirrig & Christopher R. Lamb

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

_____

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

NP, Not performed;

Table 3. Results of MR imaging

MR sequence	Intracranial inflammation group n=52 Diagnosis score					Control group n=67 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.
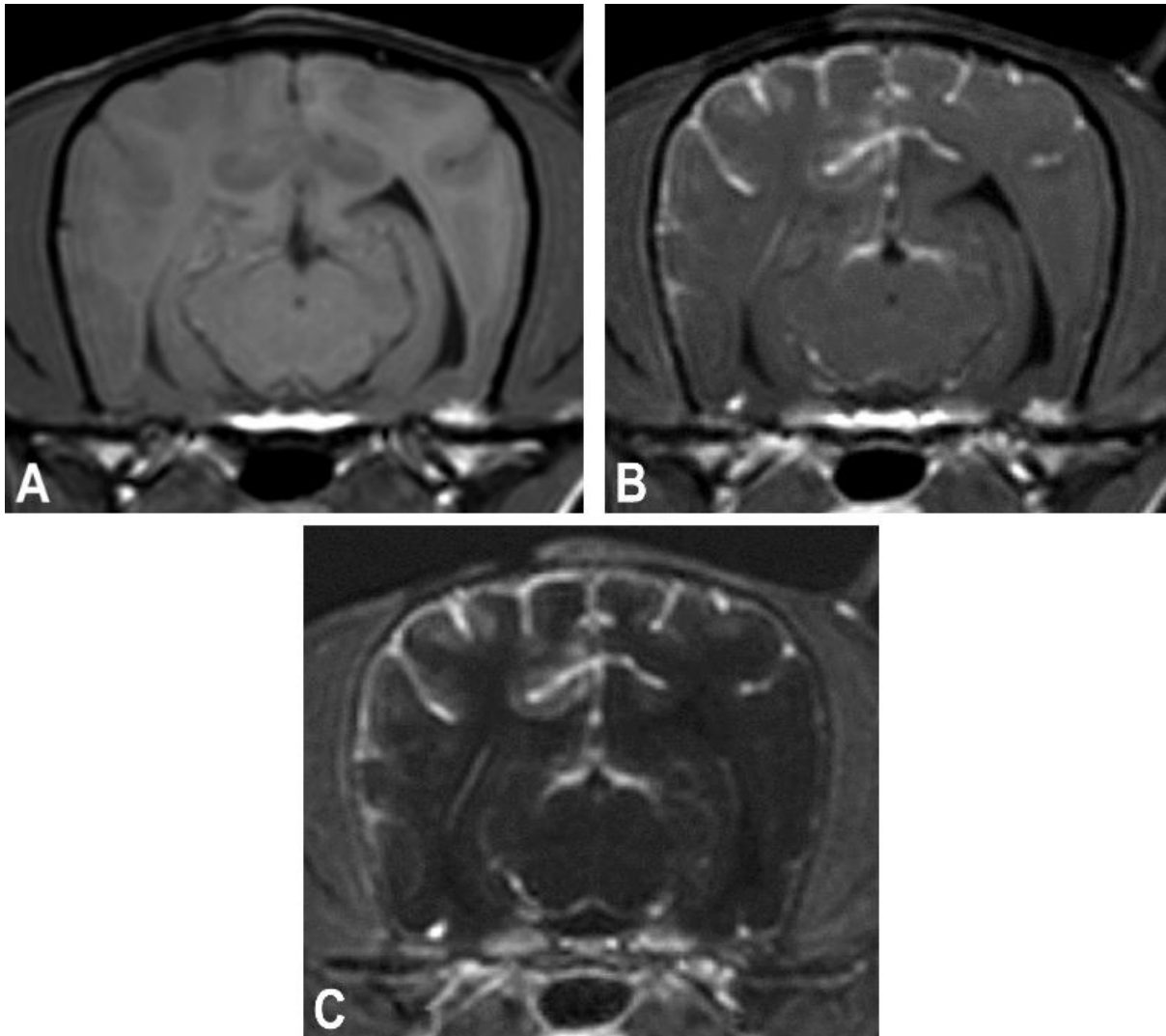
Figure 2. Different results for C-/C+ image pair and DS images in a dog with inflammatory cerebrospinal fluid and histologic diagnosis of granulomatous meningoencephalomyelitis. A) T1-weighted image, B) post-gadolinium T1-weighted image, C) corresponding DS image. There is focal moderate enhancement of the right piriform lobe in the DS image that was not recognized during review of the C-/C+ image pair.
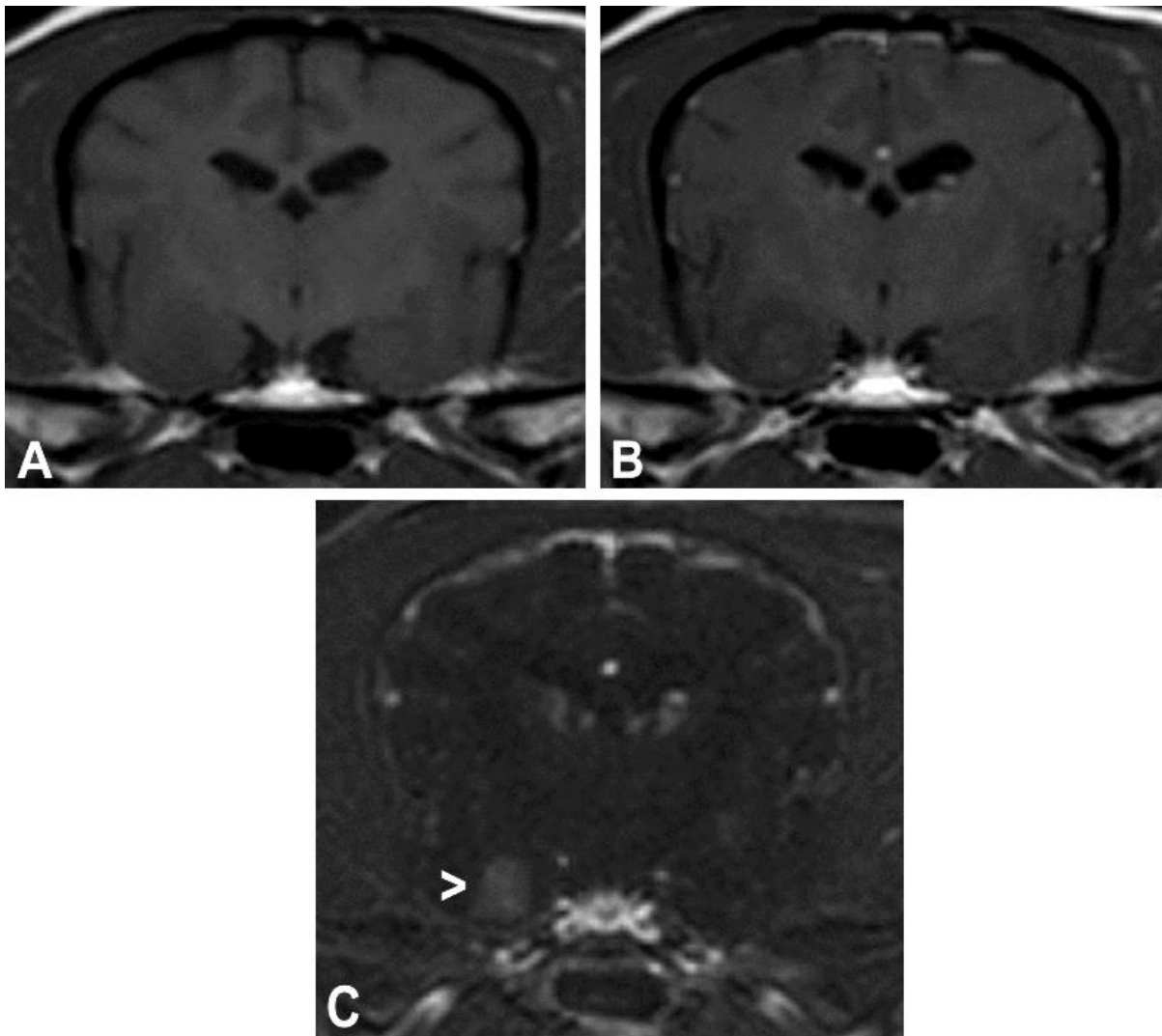
Figure 3. Examples of DS images interpreted as showing abnormal gadolinium uptake in dogs with clinical diagnosis of idiopathic epilepsy. A) Multifocal cortical enhancement (arrowheads), B) bilateral hippocampal enhancement (arrowheads), C) ependymal enhancement (arrowhead).