TITLE: CLINICAL AND MAGNETIC RESONANCE IMAGING FEATURES OF IDIOPATHIC OCULOMOTOR NEUROPATHY IN 14 DOGS

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1 **Title**

2 CLINICAL AND MAGNETIC RESONANCE IMAGING FEATURES OF

3 IDIOPATHIC OCULOMOTOR NEUROPATHY IN 14 DOGS

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32   **Key Words**

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34

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36   Canine idiopathic oculomotor neuropathy

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46   **Abstract**

47   Ophthalmoplegia/ophthalmoparesis (internal, external, or both) has been reported in dogs

48   secondary to neoplasia affecting the oculomotor nerve and is usually given a poor

49   prognosis. The purpose of this retrospective study was to describe the clinical findings,

50   magnetic resonance imaging (MRI), management, outcome and follow-up of canine cases

51   with idiopathic oculomotor neuropathy. Inclusion criteria included cases with

52   ophthalmoplegia/ophthalmoparesis (internal, external or both) as sole neuro-

53   ophthalmologic sign, complete ophthalmic and neurologic examination, head MRI, and a

54   minimum follow-up of one year. Dogs with progressive neurological signs not related

55   with oculomotor neuropathy were excluded. Fourteen cases met the inclusion criteria. All

56   cases were unilaterally affected. Magnetic resonance imaging showed equivocal

57   enlargement of the oculomotor nerve in three cases, mild enlargement in five and marked

58   enlargement in six. Contrast enhancement was present in twelve cases, being marked in

59   six. When present, the contrast enhancement was focal in eight cases and diffuse in four.

60   The median follow-up time was 25 months. External ophthalmoparesis improved in

61   seven cases, five cases under no treatment and two under systemic corticosteroid therapy.

62   The clinical signs in the other seven cases remained unchanged. Idiopathic oculomotor

63   neuropathy should be included as a differential diagnosis in dogs presenting with

64   unilateral ophthalmoplegia/ophthalmoparesis (internal, external, or both) with the

65   absence of other neurologic and ophthalmic signs, and with the MRI findings restricted to

66   the oculomotor nerve. Idiopathic oculomotor neuropathy has a good prognosis as the

67   clinical signs do not deteriorate and they can improve without treatment.

68

69   **Introduction**

70   The oculomotor nerve (cranial nerve III or CN III) innervates the ipsilateral extraocular

71   muscles (dorsal, ventral, and medial rectus and ventral oblique muscle) and the ipsilateral

72   levator palpebrae superioris muscle.[1] Additionally, CN III controls ipsilateral pupillary

73   constriction through its parasympathetic component.[1] A complete CN III lesion (motor

74   and parasympathetic dysfunction) causes areflexive mydriasis (internal ophthalmoplegia),

75   a smaller palpebral fissure due to ptosis, neuromuscular dorsolateral strabismus, and the

76   affected eye will not adduct well on testing physiological nystagmus (vestibulo-ocular

77   reflex) (external ophthalmoparesis).[2] In the veterinary literature, canine

78   ophthalmoplegia/ophthalmoparesis (internal, external, or both) has been reported

79   secondary to neoplasia affecting CN III at the level of the middle cranial fossa (MCF) or

80   orbital fissure,[3-12] and it is usually given a poor prognosis.[2] Idiopathic trigeminal and

81   facial neuropathy have been reported in dogs;[13-17] however, idiopathic oculomotor

82   neuropathy is currently not reported in the veterinary literature. The aims of this study

83   were to describe the clinical findings, magnetic resonance imaging (MRI) features,

84   management, outcome, and long-term follow-up of canine cases diagnosed with

85   idiopathic oculomotor neuropathy.

86

87   **Methods**

88   Medical records of all dogs referred to the Animal Health Trust for

89   ophthalmoplegia/ophthalmoparesis from January 1999 to December 2014 were reviewed.

90   Inclusion criteria included all cases with ophthalmoplegia/ophthalmoparesis (internal,

91   external or both) as sole neuro-ophthalmologic sign, complete ophthalmic and neurologic

92   examination, head MRI, and a minimum follow-up of one year. Dogs with progressive

93   neurological signs not related to oculomotor neuropathy were excluded.

94   Patient information collected included the following: age, gender, breed, duration of

95   clinical signs prior to referral, clinical signs and affected side at presentation, MRI

96   findings, cerebrospinal fluid (CSF) analysis, treatment, and follow-up. All MRI studies

97   were reviewed by a board-certified veterinary neurologist (E.B.) and a board-certified

98   veterinary radiologist (R.D.), who were unaware of the side of the clinical signs.

99   Disagreement was resolved by a consensus reading by the two reviewers. Five MRI

100   parameters were evaluated in each case and included the following: (1) enlargement of

101   CN III (equivocal, mild or marked), (2) intensity at the area of CN III on T2W and T1W

102   and also on FLAIR when available (hypointense, isointense or hyperintense), (3) post-

103   contrast enhancement at the area of CN III (none, mild or marked), (4) features of post-

104   contrast enhancement at the area of CN III (focal or diffuse enhancement and

105   homogenous or heterogeneous enhancement), and (5) anatomical region of the lesion.

106   The enlargement was classified as equivocal when there was uncertainty about the

107   presence or absence of enlargement, mild when the affected CN III was enlarged

108   compared to the contralateral but there was no mass effect to the surrounding neuropil,

109   and marked when the affected CN III was enlarged and there was mass effect to the

110   surrounding neuropil. The intensity of CN III on T2W was classified as hypointense

111   when its brightness was inferior to the brightness of normal gray matter, isointense when

112   its brightness was equal to the normal gray matter, and hyperintense when its brightness

113   was superior to the brightness of normal gray matter. This was repeated for T1W and also

114   for FLAIR when available. The post-contrast enhancement was categorized as mild when

115   there was contrast enhancement that was hypointense compared to the fat tissue on T1W

116   images, and marked when the contrast enhancement was isointense to the fat tissue on

117   T1W images. The contrast enhancement was classified as diffuse when detected

118   throughout the length of CN III and focal when only present at a focal location of CN III.

119   And finally, the contrast enhancement was categorized as homogenous when there was

120   uniform enhancement and heterogeneous when it was dissimilar throughout the enhanced

121   area. If follow-up MRI was available, the images were evaluated following the same

122   parameters.

123   For each patient, long term follow-up was performed with a combination of clinical re-

124   examinations, evaluation of the clinical records post-diagnosis and phone conversation

125   with the owner. The referring veterinarians were contacted for the clinical history post-

126   diagnosis of the patients. The owners whose dogs were alive at the start of the study were

127   invited for a re-examination at the Animal Health Trust. Cases re-examined received a

128   complete ophthalmic examination by a European College of Veterinary Ophthalmologists

129   trained ophthalmologist (R.T.P.) and neurological examination by board-certified

130   veterinary neurologists (C.F. and E.B.). In cases of dogs either lost to follow-up, dead or

131   not available for re-examination, the long-term follow-up was determined based on the

132   clinical records post-diagnosis and the phone conversation with the owner.

133

134   **Results**

135   *Signalment and Clinical Findings*

136   Fourteen cases met the inclusion criteria (Appendix 1). The mean (standard deviation,

137   SD) and median (range) age at presentation were 6.25 years (2.3) years and 6.5 years (3

138   to 10 years), respectively. There were entire females (n = 1, 7%), neutered females (n = 7,

139   50%), entire males (n = 2, 14%), and neutered males (n = 4, 29%). The distribution of the

140   individual breeds is shown in Appendix 1, with the more commonly affected breeds

141   being Boxer (n = 4, 29%) and Border Collie (n = 2, 14%). The mean (SD) and median

142   (range) duration of the clinical signs prior to referral were 73 days (195) and 5 days (1

143   day to 2 years), respectively. Cases presented with both internal and external

144   ophthalmoplegia/ophthalmoparesis (n = 11, 79%, Fig 1.) or only internal

145   ophthalmoplegia (n = 3, 21%). The clinical signs were unilateral in all cases, being right

146   sided (n = 8, 57%) or left sided (n = 6, 43%).

147

148   *Magnetic Resonance Imaging Findings*

149   Magnetic resonance of the head was performed using a 1.5T scanner (GE Signa, GE

150   Medical System, Milwaukee, WI, USA). Non-contiguous transverse images with a 3-5-

151   mm slice thickness and an interslice gap of 0.3-0.5 mm were generated with T1-weighted

152   (T1W) and T2-weighted (T2W) spin echo pulse sequences in all three planes. Sequences

153   included T1W and T2W and T1W with fat saturation (FAT-SAT). T1W FAT-SAT

154   images were also acquired after intravenous paramagnetic contrast medium,

155   0.05mmol/kg, gadobenate dimeglumine (Multi-Hance®, Bracco Imaging SpA, Milan

156   Italy). T1W post contrast FAT-SAT and fast fluid-attenuation inversion recovery

157   (FLAIR) findings were recorded when available. Magnetic resonance findings are

158   detailed in Appendix 2. Equivocal enlargement of CN III was noted in three cases (n = 3,

159   21%; Fig. 2), mild enlargement in five cases (n = 5, 35%; Fig. 3) and marked

160   enlargement in six cases (n = 6, 43%; Fig. 4). The affected CN III was isointense on T2W

161   and T1W pre-contrast sequences in five cases (n = 5, 35%; Fig. 2), hyperintense on T2W

162   and isointense on T1W in seven cases (n = 7, 50%; Fig. 3) and hypointense on T2W and

163   isointense on T1W in two cases (n = 2, 14%). FLAIR sequence was available in all cases

164   but in two dogs; the intensity on FLAIR was equal to T2W in all case but three cases, a

165   case with hyperintense CN III on T2W and isointense on FLAIR, and two cases with

166   isointense on T2W and hypointense on FLAIR were noted. Contrast enhancement was

167   present in all but two cases (n = 12, 86%), being marked in six cases (n = 6, 43%). When

168   present, the contrast enhancement was focal in eight cases (n = 8, 67%) and diffuse in the

169   rest (n = 4, 33%). In all cases, the anatomical region of the lesion was at the level of the

170   middle cranial fossa; however, in some cases with diffuse enhancement, the lesion

171   extended into the orbital fissure (n = 3, 21%).

172

173   *Other findings*

174   Comprehensive haematology and biochemistry were available in 13 cases and were

175   unremarkable in all. Thyroid function was evaluated in three dogs and was determined

176   within normal limits in all cases. One patient (Case 7) had been previously diagnosed

177   with hypothyroidism; however, the dog was receiving thyroid hormone supplementation

178   and the thyroid values were within normal limits at presentation. Thoracic radiographs

179   and abdominal ultrasonography were performed in seven patients and were unremarkable

180   in all. Cerebrospinal fluid was collected from the cerebellomedullary cistern in 13 dogs

181   (Appendix 1). The mean (SD) and median (range) nucleated cell count was 1.99 cells/uL

182   (2.06) and 1 cells/uL (0 to 8 cells/uL), respectively. The nucleated cell count was elevated

183   in two patients (n = 2, 14%), with 6 and 8 cells/uL (reference range 0-5 cells/uL)

184   respectively. The nucleated cellular population consisted in scattered small/medium

185   lymphocytes and monocytes in all cases, apart from Case 14 were the main population of

186   cells were hypersegmented non-degenerated neutrophils. The mean (SD) and median

187   (range) CSF total protein were 0.30 g/L (0.17) and 0.25 g/L (0.19 to 0.80 g/L),

188   respectively. The total protein was elevated in one patient (n = 1, 7%; reference range 0-

189   0.35 g/L; Case 14). Polymerase chain reaction for canine distemper virus, *Toxoplasma*

190   *gondii* and *Neospora caninum* were negative in blood and CSF in all dogs tested (n = 9,

191   64%).

192

193   *Treatment and Follow-up*

194   The treatment and follow-up information is detailed in Appendix 3. Anti-inflammatory to

195   immunosuppressive doses of systemic corticosteroid (prednisolone at 1 mg/kg once to

196   twice daily) was started at presentation in seven dogs (n = 7, 50%). Only two dogs

197   showed improvement of the clinical signs while under systemic corticosteroid treatment

198   (n = 2, 29%; Cases 4 and 14). Case 10 developed severe gastrointestinal side effects

199   within the first week of treatment and the medication was discontinued at that point. The

200   neurological signs in this dog improved three weeks after the systemic corticosteroid

201   treatment was discontinued. Case 9 showed improvement of the clinical signs three

202   months after discontinuation of the systemic corticosteroid treatment. Furthermore, three

203   dogs without systemic corticosteroid treatment (n = 3, 43%; Cases 6, 7 and 12) improved

204   two weeks to four months after their presentation. In the other seven dogs the clinical

205   signs remained unchanged, three received a course of systemic steroid therapy and four

206   had no treatment.

207   Six-month follow-up MRI scan was available in two cases (Cases 8 and 14). In case 8,

208   MRI findings at re-examination remained unchanged compared to presentation and

209   clinical signs were not improved. In case 14, MRI at presentation revealed marked

210   enlargement with marked diffuse post-contrast enhancement; however, at re-examination

211   the follow-up MRI showed equivocal enlargement with no post-contrast enhancement

212   (Fig. 5), and clinical signs were improved at that time.

213   The mean (SD) and median (range) long-term follow-up time was 33.93 months (21.76)

214   and 25 months (12 to 84 months), respectively. The external ophthalmoparesis improved

215   in 64% cases (7/11 dogs) during this period of time and the neuromuscular strabismus

216   resolved. The internal ophthalmoplegia/ophthalmoparesis remained unchanged in 79%

217   cases (11/14 dogs) and partially resolved in 21% cases (3/14 dogs). The mean (SD) and

218   median (range) time to improvement was 5.55 weeks (5.53) and 3.57 weeks (11 days to 4

219   months) respectively, from the day the clinical signs were first noted. Follow-up of over

220   one year with complete ophthalmic and neurological re-examination by the authors was

221   possible in six cases.

222

223   **Discussion**

224   This is the first descriptive study of idiopathic oculomotor neuropathy in dogs. The

225   presumptive diagnosis of idiopathic neuropathy was made in all cases based on the failure

226   on revealing an underlying cause. A putative association between cranial neuropathy and

227   hypothyroidism has been stated in the veterinary literature,[18,19] however this is not borne

228   out by other studies.[17,20] None of the dogs of this study showed clinical signs of

229   hypothyroidism and the thyroidal function was normal in the three dogs tested. One case

230 had been previously diagnosed with hypothyroidism; however, the authors think that

231 there is unlikely association between the hypothyroidism and the oculomotor neuropathy

232 due to the fact that at the time of the onset of the clinical signs (oculomotor neuropathy)

233 the dog did not reveal any clinical signs consistent with hypothyroidism and the thyroid

234 function was controlled. Infectious causes of neuropathy are exceptionally rare in dogs,[2]

235 and none of the dogs tested in this report for canine distemper virus, *Toxoplasma gondii*

236 and *Neospora caninum* were positive. In this study, the lack of clinical deterioration in all

237 cases and the clinical improvement in several dogs might indicate the presence of an

238 underlying oculomotor neuritis with subsequent permanent nerve damage. Furthermore,

239 the MRI findings (CN III enlargement with contrast enhancement) and the mildly

240 elevated cell count in CSF (in two dogs) could support this hypothesis. However, this

241 hypothesis could not be confirmed due to the lack of histopathology and for this reason

242 the term idiopathic neuropathy was adopted. Surgical biopsy at this area carries high

243 operative morbidity due to the location and to the authors' knowledge this surgical

244 approach has not been attempted in dogs.

245 All cases in this study presented with mydriasis, and only two dogs retained some

246 pupillary response to light at presentation. On the other hand, external ophthalmoparesis

247 was only seen in some dogs. The oculomotor parasympathetic axons are located

248 superficially on the medial side of CN III,[1] subsequently if the neuropathy initiates in this

249 location it is likely that only the parasympathetic component will be affected. The clinical

250 signs were unilateral in all dogs in this study, similar to the reported canine cases of

251 idiopathic facial neuropathy but different to trigeminal neuropathy.[13-17] There are several

252 cases published of unilateral idiopathic trigeminal neuropathy in dogs,[21] however the

253   majority are bilaterally affected.[13] Bilateral trigeminal neuropathy commonly presents

254   with sudden inability to close the mouth;[13] on the other hand, unilateral trigeminal

255   neuropathy may only manifest with unilateral transitory masticatory muscle atrophy.[2]

256   Subsequently, it is possible that unilateral cases of trigeminal neuropathy of the

257   mandibular branch are overlooked by owners and veterinarians if the atrophy is mild or

258   transitory. The mean recovery time of motor function was five weeks in the present

259   study, similar to other idiopathic cranial neuropathies;[13,14,16] however, a third of the cases

260   affected with CN III motor dysfunction (4/11 dogs) in our study showed no signs of

261   improvement. This finding differs from trigeminal neuropathy where the motor function

262   recovered in all cases;[13] but similar to facial neuropathy, where resolution of clinical

263   signs was only seen in half of the affected dogs.[14,15,16] Some degree of mydriasis persisted

264   in all cases in our study; however, almost a quarter of patients recovered partial CN III

265   parasympathetic function. Medical treatment with corticosteroids did not appear to alter

266   the course of the disease in this study, even though the dose used and length of course

267   varied. Further studies are required to prove the efficacy of corticosteroids for the

268   treatment of idiopathic oculomotor neuropathy, however corticosteroid therapy does not

269   appear to change the clinical outcome of other cranial neuropathies.[13,22]

270   A total of 22 cases of canine ophthalmoplegia/ophthalmoparesis (internal, external or

271   both) are published in the veterinary literature.[3-12] Of these 22 cases, only three report

272   isolated CN III deficits,[5,8,10] the rest of the reports describe dogs with multiple cranial

273   nerve dysfunction as part of middle cranial fossa syndrome (also known as cavernous

274   sinus syndrome) or other neurological signs.[3-7,9,11,12] The middle cranial fossa is a paired

275   depression of the basiphenoid bone, located between the rostral and caudal cranial fossa

276   at the base of the skull.[1] Multiple cranial nerves travel through the middle cranial fossa

277   including the oculomotor, trochlear and abducens nerves, as well as the three branches of

278   the trigeminal nerve.[1] These cranial nerves exit/enter the skull through the orbital fissure

279   (oculomotor nerve, trochlear nerve, abducens nerve and ophthalmic branch of the

280   trigeminal nerve), round foramen (maxillary branch of the trigeminal nerve), or oval

281   foramen (mandibular branch of the trigeminal nerve).[1] The middle cranial fossa

282   syndrome is a well-recognised syndrome in dogs characterised by variable impairment of

283   these nerves.[2] In the veterinary literature, this syndrome is usually referred to as

284   cavernous sinus syndrome.[3,4,6,7,9,10] However, this term should ideally be discarded,

285   because these cranial nerves are not directly related to the cavernous sinus.[2] Twelve of 22

286   dogs published in the veterinary literature showed unilateral deficits,[3-8,10-12] two cases

287   presented with unilateral signs and became bilateral within days,[4,6] and six cases had

288   bilateral deficits at presentation.[4,5,9] All cases were reported to be secondary to neoplasia

289   at the level of the middle cranial fossa or orbital fissure.[3-12] Ten dogs were euthanized at

290   presentation,[3-5,7,10,12] and for the rest, the mean life expectancy after diagnosis was 7.1

291   months[3,4,6,8-10] with the longest survival time of 18 months.[6] Clinical signs deteriorated

292   over this period of time in all cases, precipitating euthanasia.[3,4,6,8-10] For this reason, the

293   inclusion criteria of the current study demanded a minimal follow-up time of 12 months

294   and only dogs with no deterioration of the neurological signs were included.

295   Magnetic resonance is the diagnostic imaging modality of choice in veterinary medicine

296   for diseases affecting cranial nerves.[23] Magnetic resonance provides superior resolution

297   of the retrobulbar and intracranial CN III pathway compared to computed tomography.[23]

298   In this study, MRI enabled an accurate and detailed morphological assessment of the

299 lesions in all cases, only two dogs had equivocal enlargement of the CN III and no post-

300 contrast enhancement on MRI. Localization and extension of the lesions were in

301 accordance with the neuroanatomic localization is all cases, and six months follow-up

302 MRI was possible in two. Based upon the location, shape, invasiveness, signal intensity,

303 homogeneity, and enhancement properties of the lesion, MRI features can help the

304 differentiation between neoplastic and inflammatory disorders in cranial nerves

305 dysfunction.[21,24,25] Human patients that have cranial nerve enhancement following

306 contrast medium administration, but do not have an associated mass are considered to

307 have cranial neuritis or ganglionitis rather than neoplasia.[25] Similarly in veterinary

308 medicine, dogs with trigeminal neuritis confirmed postmortem had diffuse enlargement

309 of the nerve without a mass lesion.[21] In the present study, six cases had marked

310 enlargement of the CN III with mass effect in the surrounding tissue; three of these had

311 diffuse enhancement in most of the length of the CN III, and the other marked focal

312 enlargement of the nerve that could be considered a neoplastic lesion based on previously

313 published literature. The pathogenesis of the disease in this study remains currently

314 obscure, however, no deterioration of the clinical sings, no involvement of other cranial

315 nerves or general condition was noted in any the dogs with a follow-up time of 20 to 41

316 months, which would be expected with a neoplastic lesion over that length of time.

317 Therefore, we could conclude that idiopathic oculomotor neuropathy is not indicative of a

318 serious underlying disorder.

319 The main limitations of this study include the low number of cases, lack of pathologic

320 confirmation, lack of standardized MRI protocols and heterogeneous nature of the study

321 design. Results could be more definitively supported with a prospective multi-center

322   study. Futures studies could also evaluate the sensitivity and specificity of MRI for

323   detecting CN III abnormalities in dogs with idiopathic oculomotor neuropathy. Moreover,

324   MRI features (including a more objective measurement for cranial nerve enlargement)

325   could be evaluated as prognostic factors for regaining full CN III function. The lack of

326   histopathology was unavoidable due to the non-fatal nature of this condition and the high

327   morbidity that a surgical biopsy could carry due to the location of the lesion. The authors

328   applied stringent inclusion criteria for sampled animals in the current study in order to

329   maximize the likelihood of a true positive diagnosis as much as possible.

330

331   In conclusion, findings from the current study supported including idiopathic oculomotor

332   neuropathy as a differential diagnosis for dogs presenting with unilateral

333   ophthalmoplegia/ophthalmoparesis (internal, external, or both) with the absence of other

334   neurological and ophthalmic signs, and with MRI lesions restricted to CN III. These cases

335   can have a good prognosis as the clinical signs do not deteriorate or can even improve

336   without treatment.

337

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339   Category 1

340   (a) Conception and Design: Elsa Beltran, Roser Tetas Pont and Courtenay Freeman

341   (b) Acquisition of Data: Roser Tetas Pont, Courtenay Freeman and Elsa Beltran

342   (c) Analysis and Interpretation of Data: Roser Tetas Pont, Courtenay Freeman, Elsa

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348 Category 3

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419

420

421 **Appendices**

422 Appendix 1. Clinical Findings for Dogs with Ophthalmoplegia/ophthalmoparesis and

423 Presumed Idiopathic Oculomotor Neuropathy.

Case	Signalment (Breed age sex)	Duration clinical signs (days)	Side of clinical signs	Parasympathetic component CNIII	Motor component CNIII	CSF nucleated cell count (cells/uL)	CSF total protein (g/L)
1	Gh 10y MN	5	Left	Plegia	Not affected	0	0.24
2	BC 8y FN	7	Right	Plegia	Not affected	Not available	Not available
3	BT 4y FN	30	Right	Plegia	Not affected	1	0.25
4	Bx 5y ME	5	Right	Paresis	Paresis	0	0.25
5	RC 5y MN	5	Right	Paresis	Paresis	0	0.19
6	Bx 3y FE	4	Right	Plegia	Paresis	8	0.24
7	Bx 7y FN	14	Left	Plegia	Paresis	6	0.24
8	LR 4y FN	180	Left	Plegia	Paresis	1	0.27
9	Bx 8y FN	4	Right	Plegia	Paresis	1	0.31
10	GR 7y MN	1	Left	Plegia	Paresis	0.9	0.22
11	Be 6y MN	30	Right	Plegia	Paresis	4	0.32
12	SBT 9.5y ME	2	Left	Plegia	Paresis	0	0.28
13	BC 7y FN	30/730*	Right	Plegia	Plegia	4	0.35
14	We 3.5y FN	5	Left	Plegia	Plegia	0	0.80

424

425 *Footnote:* Be, Beagle; BC, Border Collie; BT, Border Terrier; Bx, Boxer; CNIII, third

426 cranial nerve; CSF, cerebrospinal fluid; FE, female entire; FN, female neutered; Gh,

427   Greyhound; GR, Golden Retriever; LR, Labrador Retriever; ME, male entire; MN, male

428   neutered; RC, Rough Collie; SBT, Staffordshire Bull Terrier; We, Weimaraner.

429   *, in Case 13 the mydriasis was noted a month prior to presentation and the

430   neuromuscular strabismus two years before.

431

432

433

434   Appendix 2. Magnetic Resonance Findings for Dogs with

435   Ophthalmoplegia/ophthalmoparesis Associated with Presumed Idiopathic Oculomotor

436   Neuropathy.

437

Case	Side of MRI findings	Enlargement CNIII	Intensity of CNIII in			Degree of contrast enhancement	Appearance of contrast enhancement	Anatomical area of the lesion
			T2W	FLAIR	T1W			
1	Left	Marked	Hyper	Hyper	Iso	Marked	Diffuse and heterogeneous	MCF
2	Right	Equivocal	Iso	Iso	Iso	No enhancement	No enhancement	MCF
3	Right	Mild	Iso	Iso	Iso	Mild	Focal and homogeneous	MCF
4	Right	Marked	Hyper	Iso	Iso	Marked	Diffuse and heterogeneous	OF and MCF
5	Right	Equivocal	Hyper	N/A	Iso	Mild	Focal and homogeneous	MCF
6	Right	Mild	Hyper	Hyper	Iso	Mild	Focal and homogeneous	MCF
7	Left	Mild	Hyper	Hyper	Iso	Mild	Focal and heterogeneous	MCF
8	Left	Marked	Hypo	Hypo	Iso	Marked	Focal and homogeneous	MCF
9	Right	Marked	Hyper	N/A	Iso	Marked	Focal and heterogeneous	MCF
10	Left	Equivocal	Iso	Iso	Iso	No enhancement	No enhancement	MCF
11	Right	Marked	Iso	Hypo	Iso	Marked	Focal and homogeneous	MCF
12	Left	Mild	Hyper	Hyper	Iso	Mild	Diffuse and homogenous	OF and MCF
13	Right	Mild	Hypo	Hypo	Iso	Mild	Focal and homogeneous	MCF
14	Left	Marked	Iso	Hypo	Iso	Marked	Diffuse and homogenous	OF and MCF

438

439   *Footnote:* CNIII, third cranial nerve (oculomotor nerve); Hyper, hyperintensive; Hypo,

440   hypointensive; Iso, isointense; MCF, middle cranial fossa; MRI, magnetic resonance

441   imaging; N/A, not available; OF, orbital fissure.

442

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445 Appendix 3. Treatment, Progression and Follow-up for Dogs with

446 Ophthalmoplegia/ophthalmoparesis Associated with Idiopathic Oculomotor Neuropathy.

447

Case	Systemic corticosteroid treatment	Progression clinical signs during the FU period (CNIII motor and parasympathetic components)	Long term FU (months)	Reason for lost FU
1	No	Unchanged	24	Lost to FU
2	No	Unchanged	77	End of study
3	Prednisolone 1 mg/kg BID for 3w then taping down	Unchanged	39	End of study
4	Prednisolone 1 mg/kg BID for 3w then taping down	Motor and parasympathetic components at 1w post referral	18	Lost to FU
5	No	Unchanged	24	Lost to FU
6	No	Motor and parasympathetic components at 3w post referral	84	Death for unrelated reasons
7	No	Motor component at 3w post referral	42	Death for unrelated reasons
8	No	Unchanged	26	Lost to FU
9	Prednisolone 1 mg/kg SID for 2w then taping down	Motor component at 4m post referral (already off treatment)	41	Death for unrelated reasons
10	Prednisolone 1 mg/kg SID for 1w then discontinue	Motor component at 1m post referral (already off treatment)	20	End of study
11	Prednisolone 1 mg/kg BID for 2w then taping down	Unchanged	20	End of study
12	No	Motor component at 2w post referral	12	End of study
13	Prednisolone 1 mg/kg SID for 1m then taping down	Unchanged	18	Death for unrelated reasons
14	Prednisolone 1 mg/kg SID for 1m then taping down	Motor and parasympathetic components at 1m post referral	30	End of study

448   *Footnote:* CNIII, third cranial nerve (oculomotor nerve); FU, follow-up; MRI, magnetic

449   resonance imaging.

450

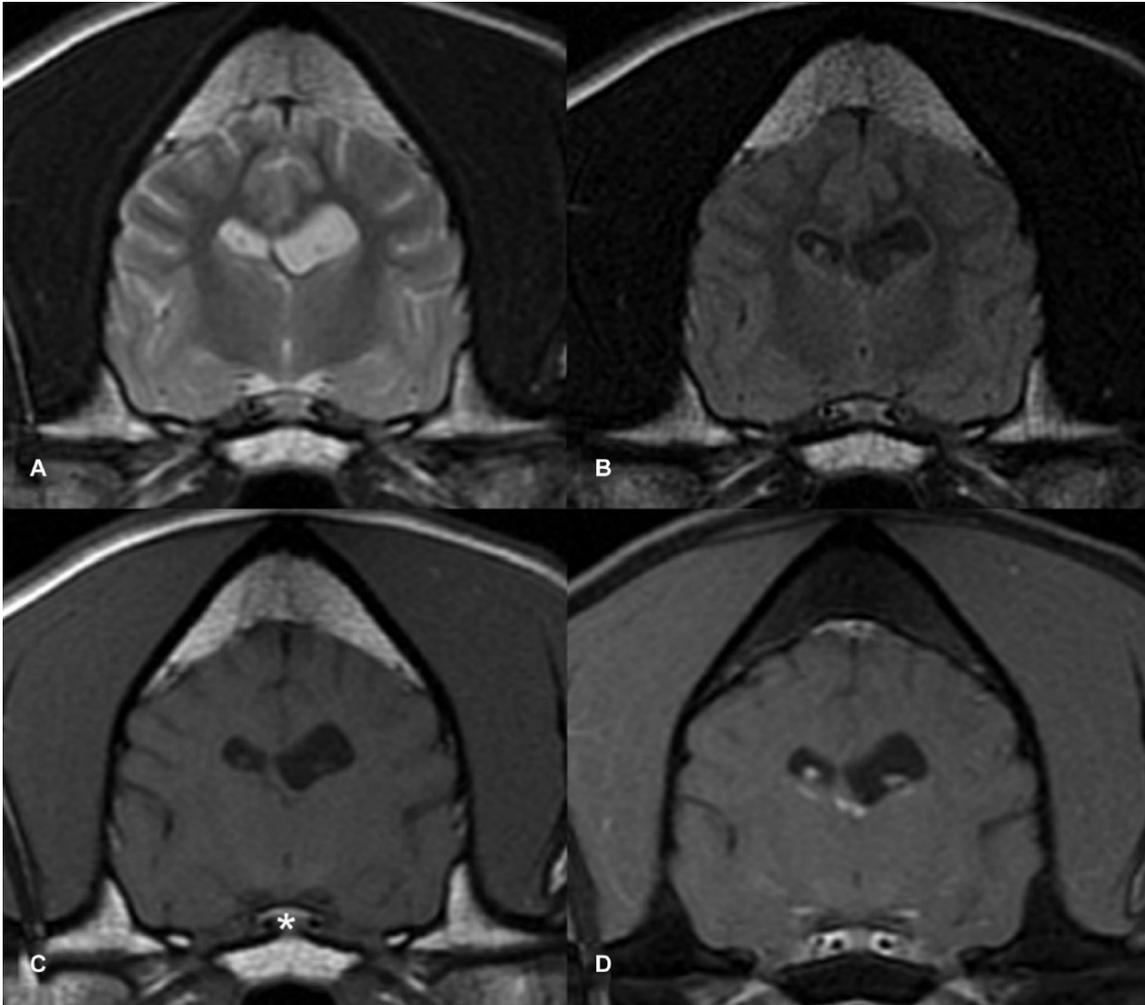451

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453 **Figure legends**

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457 Figure 1. Mydriasis secondary to internal ophthalmoplegia, and upper eyelid ptosis and

458 neuromuscular strabismus (dorsolateral) secondary to external ophthalmoparesis of the

459 left eye in a nine and a half-year-old male entire Staffordshire Bull Terrier (Case 12).

460

Figure 2. Transverse magnetic resonance images obtained at the level of the pituitary gland (asterisk) in a seven-year-old male neutered Golden Retriever presented with internal ophthalmoplegia and external ophthalmoparesis of the left eye (Case 10). There is equivocal enlargement and isointensity of the left oculomotor nerve on T2W (A), on FLAIR (B), and on T1W pre-contrast (C) with no enhancement of left oculomotor following contrast administration (D).
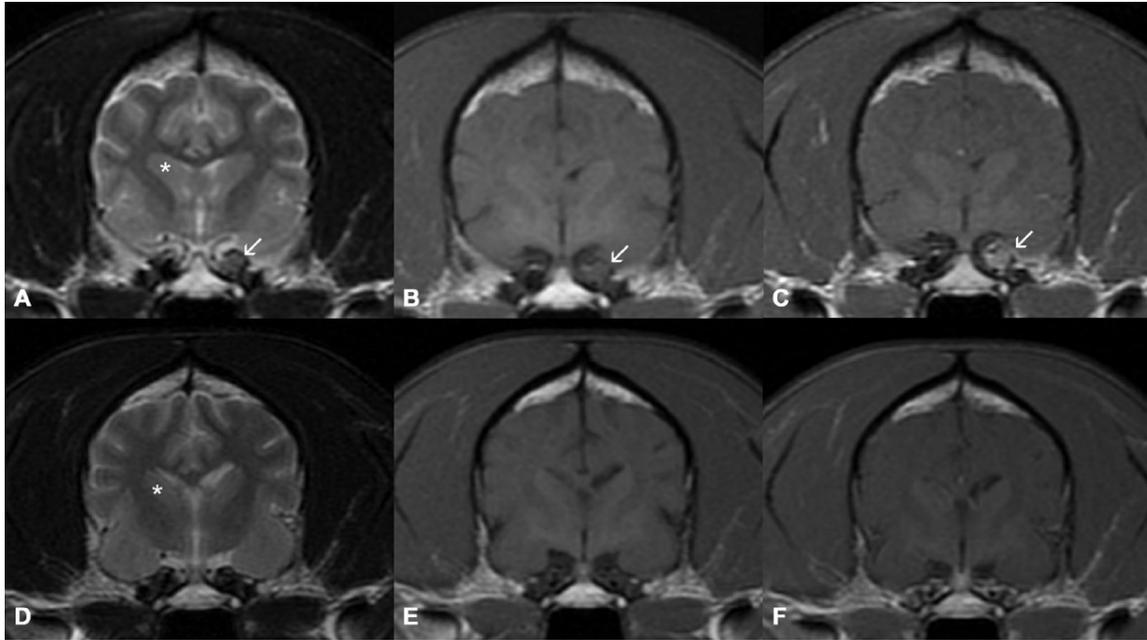
469
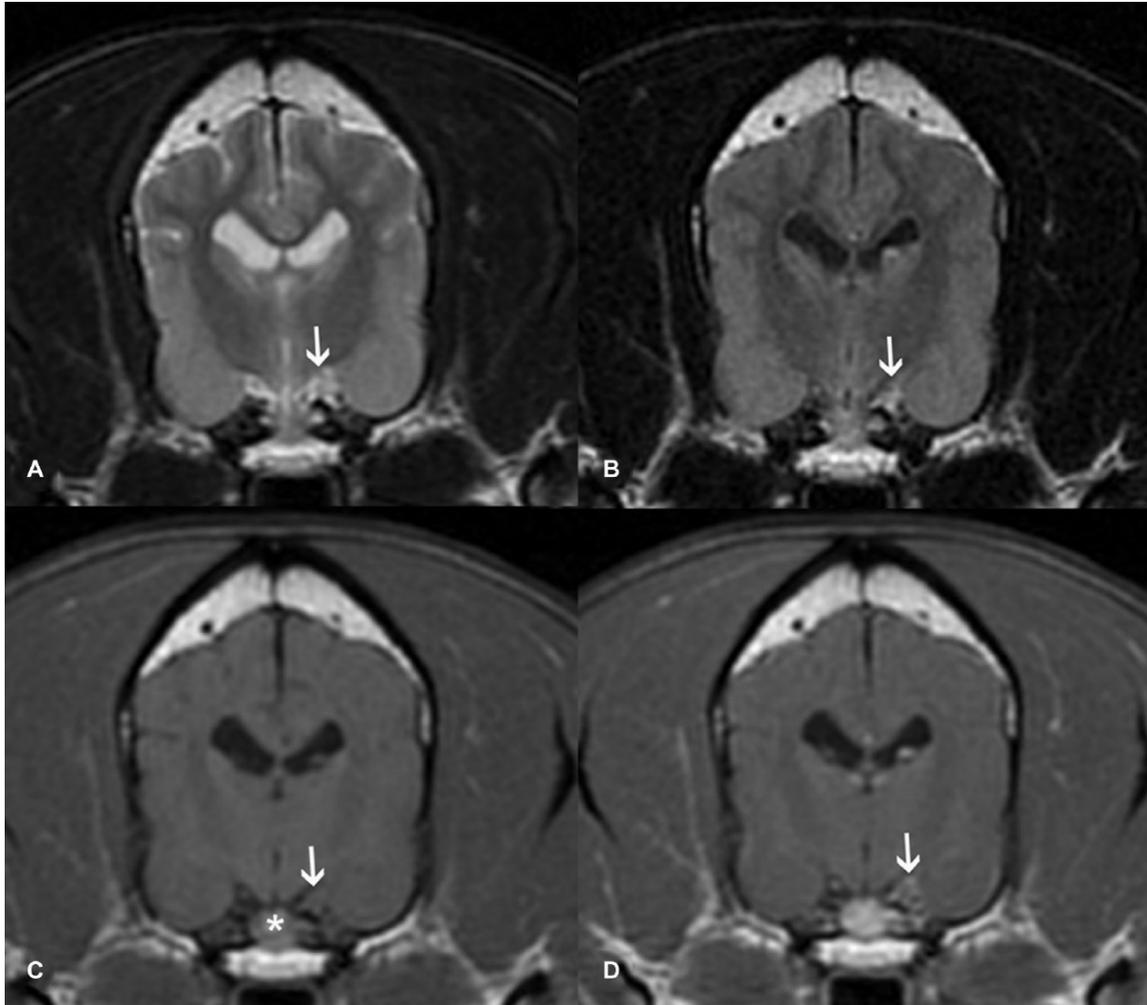
Figure 3. Transverse magnetic resonance images obtained at the level of the pituitary

gland (asterisk) in a seven-year-old female neutered Boxer presented with internal

ophthalmoplegia and external ophthalmoparesis of the left eye (Case 7). There is mild

enlargement of the left oculomotor nerve with hyperintensity on T2W (arrow; A),

hyperintensity on FLAIR (arrow; B), and isointensity on T1W pre-contrast (arrow; C)

with mild focal heterogeneous enhancement following contrast administration (arrow; D).
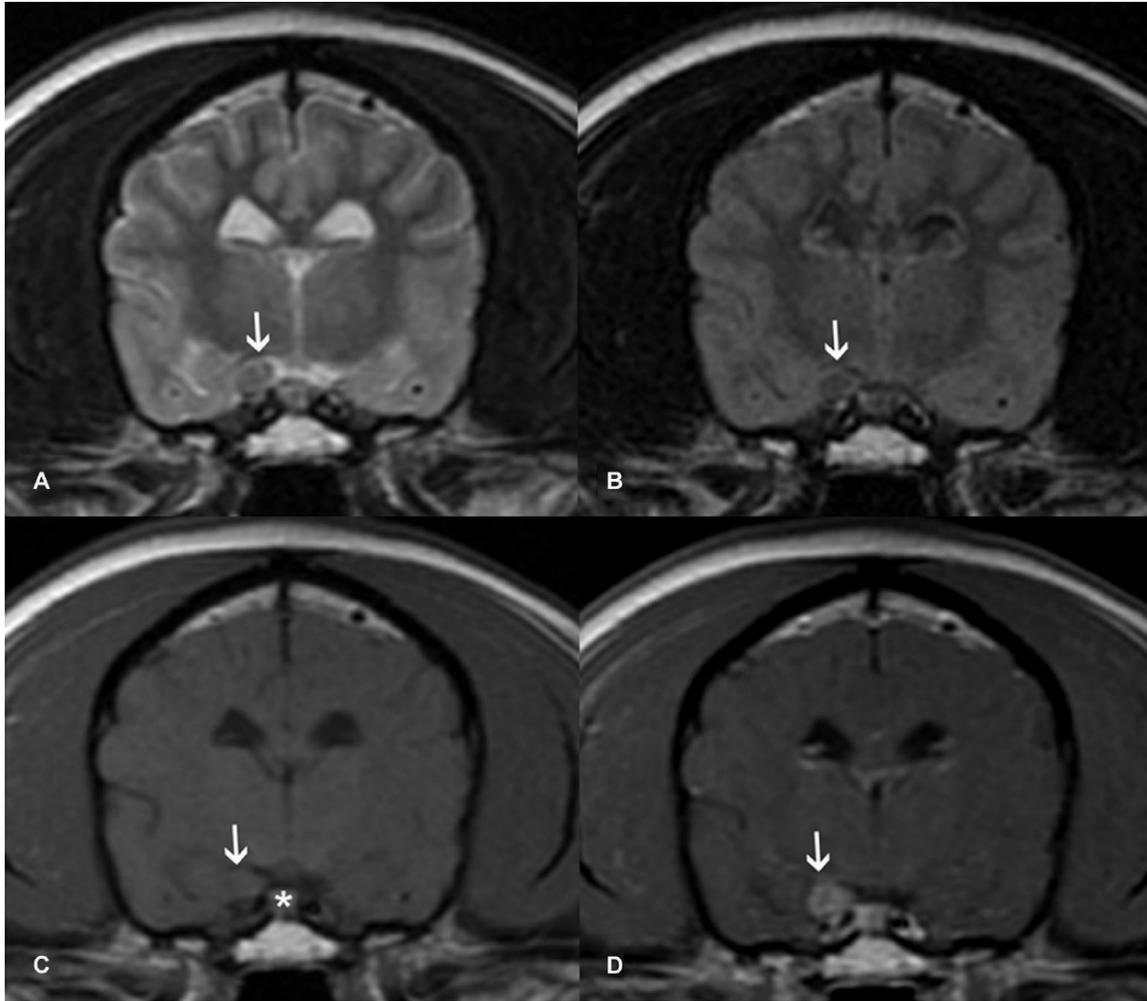
476

477 Figure 4. Transverse magnetic resonance images obtained at the level of the pituitary

478 gland (asterisk) in a six-year-old male neutered Beagle presented with internal

479 ophthalmoplegia and external ophthalmoparesis of the right eye (Case 11). There is

480 marked enlargement of the right oculomotor nerve with isointensity on T2W (arrow; A),

481 hypointensity on FLAIR (arrow; B), and isointensity on T1W pre-contrast (arrow; C)

482 with marked focal homogeneous enhancement following contrast administration (arrow;

483 D).

484

485

486 Figure 5. Transverse magnetic resonance images obtained at the level of the head of the

487 caudate nucleus (asterisk) in a three and a half-year-old female neutered Weimaraner

488 presented with internal ophthalmoplegia and external ophthalmoparesis of the left eye

489 (Case 14). There is marked enlargement of the left oculomotor nerve with isointensity on

490 T2W (arrow; A) and isointensity on T1W pre-contrast (arrow; B), with marked diffuse

491 homogeneous enhancement following contrast administration (arrow; C) at presentation.

492 At six-moth follow-up scan, there is resolution of the magnetic resonance findings (D-F).

493