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

AUTHORS: Roser Tetas Pont, Courtenay Freeman, Ruth Dennis, Claudia Hartley, Elsa Beltran

JOURNAL: VETERINARY RADIOLOGY & ULTRASOUND

PUBLISHER: Wiley

PUBLICATION DATE: May/June 2017

DOI: 10.1111/vru.12478

Title

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

Authors

Roser Tetas Pont. Comparative Ophthalmology Unit, Animal Health Trust, Lanwades Park, Kentford CB8 7UU United Kingdom. Current address: Queen Mother Hospital for Animals. Royal Veterinary College. Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA United Kingdom. rtetas@rvc.ac.uk

Courtenay Freeman. Neurology/Neurosurgery Unit, Animal Health Trust, Lanwades Park, Kentford CB8 7UU United Kingdom. Current address: Veterinary Specialty Care, 985 Johnnie Dodds Blvd, Mount Pleasant, SC 29464.
cfreeman@veterinaryspecialtycare.com

Ruth Dennis. Diagnostic Imaging Unit, Animal Health Trust, Lanwades Park, Kentford CB8 7UU United Kingdom. ruth.dennis@aht.org.uk

Claudia Hartley. Comparative Ophthalmology Unit, Animal Health Trust, Lanwades Park, Kentford CB8 7UU United Kingdom. Current address: Davies Veterinary Specialists, Manor Farm Business Park, Higham Gobion, Herts SG5 3HR United Kingdom. chartley@vetspecialists.co.uk

Elsa Beltran. Neurology/Neurosurgery Unit, Animal Health Trust, Lanwades Park, Kentford CB8 7UU United Kingdom. Current address: Queen Mother Hospital for Animals. Royal Veterinary College. Hawkshead Lane, North Mymms, Hertfordshire AL9 7TA United Kingdom. ebeltran@rvc.ac.uk

Corresponding address

Roser Tetas Pont

rtetas@rvc.ac.uk

Key Words

canine, ophthalmoplegia, oculomotor nerve, MRI, CNIII

Running head

Canine idiopathic oculomotor neuropathy

Abstract

Ophthalmoplegia/ophthalmoparesis (internal, external, or both) has been reported in dogs secondary to neoplasia affecting the oculomotor nerve and is usually given a poor prognosis. The purpose of this retrospective study was to describe the clinical findings, magnetic resonance imaging (MRI), management, outcome and follow-up of canine cases with idiopathic oculomotor neuropathy. Inclusion criteria included cases with ophthalmoplegia/ophthalmoparesis (internal, external or both) as sole neuro-ophthalmologic sign, complete ophthalmic and neurologic examination, head MRI, and a minimum follow-up of one year. Dogs with progressive neurological signs not related with oculomotor neuropathy were excluded. Fourteen cases met the inclusion criteria. All cases were unilaterally affected. Magnetic resonance imaging showed equivocal enlargement of the oculomotor nerve in three cases, mild enlargement in five and marked enlargement in six. Contrast enhancement was present in twelve cases, being marked in six. When present, the contrast enhancement was focal in eight cases and diffuse in four. The median follow-up time was 25 months. External ophthalmoparesis improved in seven cases, five cases under no treatment and two under systemic corticosteroid therapy. The clinical signs in the other seven cases remained unchanged. Idiopathic oculomotor neuropathy should be included as a differential diagnosis in dogs presenting with unilateral ophthalmoplegia/ophthalmoparesis (internal, external, or both) with the absence of other neurologic and ophthalmic signs, and with the MRI findings restricted to the oculomotor nerve. Idiopathic oculomotor neuropathy has a good prognosis as the clinical signs do not deteriorate and they can improve without treatment.

Introduction

The oculomotor nerve (cranial nerve III or CN III) innervates the ipsilateral extraocular muscles (dorsal, ventral, and medial rectus and ventral oblique muscle) and the ipsilateral levator palpebrae superioris muscle.[1] Additionally, CN III controls ipsilateral pupillary constriction through its parasympathetic component.[1] A complete CN III lesion (motor and parasympathetic dysfunction) causes areflexive mydriasis (internal ophthalmoplegia), a smaller palpebral fissure due to ptosis, neuromuscular dorsolateral strabismus, and the affected eye will not adduct well on testing physiological nystagmus (vestibulo-ocular reflex) (external ophthalmoparesis).[2] In the veterinary literature, canine ophthalmoplegia/ophthalmoparesis (internal, external, or both) has been reported secondary to neoplasia affecting CN III at the level of the middle cranial fossa (MCF) or orbital fissure,[3-12] and it is usually given a poor prognosis.[2] Idiopathic trigeminal and facial neuropathy have been reported in dogs;[13-17] however, idiopathic oculomotor neuropathy is currently not reported in the veterinary literature. The aims of this study were to describe the clinical findings, magnetic resonance imaging (MRI) features, management, outcome, and long-term follow-up of canine cases diagnosed with idiopathic oculomotor neuropathy.

Methods

Medical records of all dogs referred to the Animal Health Trust for ophthalmoplegia/ophthalmoparesis from January 1999 to December 2014 were reviewed. Inclusion criteria included all cases with ophthalmoplegia/ophthalmoparesis (internal, external or both) as sole neuro-ophthalmologic sign, complete ophthalmic and neurologic

examination, head MRI, and a minimum follow-up of one year. Dogs with progressive neurological signs not related to oculomotor neuropathy were excluded.

Patient information collected included the following: age, gender, breed, duration of clinical signs prior to referral, clinical signs and affected side at presentation, MRI findings, cerebrospinal fluid (CSF) analysis, treatment, and follow-up. All MRI studies were reviewed by a board-certified veterinary neurologist (E.B.) and a board-certified veterinary radiologist (R.D.), who were unaware of the side of the clinical signs. Disagreement was resolved by a consensus reading by the two reviewers. Five MRI parameters were evaluated in each case and included the following: (1) enlargement of CN III (equivocal, mild or marked), (2) intensity at the area of CN III on T2W and T1W and also on FLAIR when available (hypointense, isointense or hyperintense), (3) post-contrast enhancement at the area of CN III (none, mild or marked), (4) features of post-contrast enhancement at the area of CN III (focal or diffuse enhancement and homogenous or heterogeneous enhancement), and (5) anatomical region of the lesion. The enlargement was classified as equivocal when there was uncertainty about the presence or absence of enlargement, mild when the affected CN III was enlarged compared to the contralateral but there was no mass effect to the surrounding neuropil, and marked when the affected CN III was enlarged and there was mass effect to the surrounding neuropil. The intensity of CN III on T2W was classified as hypointense when its brightness was inferior to the brightness of normal gray matter, isointense when its brightness was equal to the normal gray matter, and hyperintense when its brightness was superior to the brightness of normal gray matter. This was repeated for T1W and also for FLAIR when available. The post-contrast enhancement was categorized as mild when

there was contrast enhancement that was hypointense compared to the fat tissue on T1W images, and marked when the contrast enhancement was isointense to the fat tissue on T1W images. The contrast enhancement was classified as diffuse when detected throughout the length of CN III and focal when only present at a focal location of CN III. And finally, the contrast enhancement was categorized as homogenous when there was uniform enhancement and heterogeneous when it was dissimilar throughout the enhanced area. If follow-up MRI was available, the images were evaluated following the same parameters.

For each patient, long term follow-up was performed with a combination of clinical re-examinations, evaluation of the clinical records post-diagnosis and phone conversation with the owner. The referring veterinarians were contacted for the clinical history post-diagnosis of the patients. The owners whose dogs were alive at the start of the study were invited for a re-examination at the Animal Health Trust. Cases re-examined received a complete ophthalmic examination by a European College of Veterinary Ophthalmologists trained ophthalmologist (R.T.P.) and neurological examination by board-certified veterinary neurologists (C.F. and E.B.). In cases of dogs either lost to follow-up, dead or not available for re-examination, the long-term follow-up was determined based on the clinical records post-diagnosis and the phone conversation with the owner.

Results

Signalment and Clinical Findings

Fourteen cases met the inclusion criteria (Appendix 1). The mean (standard deviation, SD) and median (range) age at presentation were 6.25 years (2.3) years and 6.5 years (3

to 10 years), respectively. There were entire females (n = 1, 7%), neutered females (n = 7, 50%), entire males (n = 2, 14%), and neutered males (n = 4, 29%). The distribution of the individual breeds is shown in Appendix 1, with the more commonly affected breeds being Boxer (n = 4, 29%) and Border Collie (n = 2, 14%). The mean (SD) and median (range) duration of the clinical signs prior to referral were 73 days (195) and 5 days (1 day to 2 years), respectively. Cases presented with both internal and external ophthalmoplegia/ophthalmoparesis (n = 11, 79%, Fig 1.) or only internal ophthalmoplegia (n = 3, 21%). The clinical signs were unilateral in all cases, being right sided (n = 8, 57%) or left sided (n = 6, 43%).

Magnetic Resonance Imaging Findings

Magnetic resonance of the head was performed using a 1.5T scanner (GE Signa, GE Medical System, Milwaukee, WI, USA). Non-contiguous transverse images with a 3-5-mm slice thickness and an interslice gap of 0.3-0.5 mm were generated with T1-weighted (T1W) and T2-weighted (T2W) spin echo pulse sequences in all three planes. Sequences included T1W and T2W and T1W with fat saturation (FAT-SAT). T1W FAT-SAT images were also acquired after intravenous paramagnetic contrast medium, 0.05mmol/kg, gadobenate dimeglumine (Multi-Hance®, Bracco Imaging SpA, Milan Italy). T1W post contrast FAT-SAT and fast fluid-attenuation inversion recovery (FLAIR) findings were recorded when available. Magnetic resonance findings are detailed in Appendix 2. Equivocal enlargement of CN III was noted in three cases (n = 3, 21%; Fig. 2), mild enlargement in five cases (n = 5, 35%; Fig. 3) and marked enlargement in six cases (n = 6, 43%; Fig. 4). The affected CN III was isointense on T2W

and T1W pre-contrast sequences in five cases (n = 5, 35%; Fig. 2), hyperintense on T2W and isointense on T1W in seven cases (n = 7, 50%; Fig. 3) and hypointense on T2W and isointense on T1W in two cases (n = 2, 14%). FLAIR sequence was available in all cases but in two dogs; the intensity on FLAIR was equal to T2W in all case but three cases, a case with hyperintense CN III on T2W and isointense on FLAIR, and two cases with isointense on T2W and hypointense on FLAIR were noted. Contrast enhancement was present in all but two cases (n = 12, 86%), being marked in six cases (n = 6, 43%). When present, the contrast enhancement was focal in eight cases (n = 8, 67%) and diffuse in the rest (n = 4, 33%). In all cases, the anatomical region of the lesion was at the level of the middle cranial fossa; however, in some cases with diffuse enhancement, the lesion extended into the orbital fissure (n = 3, 21%).

Other findings

Comprehensive haematology and biochemistry were available in 13 cases and were unremarkable in all. Thyroid function was evaluated in three dogs and was determined within normal limits in all cases. One patient (Case 7) had been previously diagnosed with hypothyroidism; however, the dog was receiving thyroid hormone supplementation and the thyroid values were within normal limits at presentation. Thoracic radiographs and abdominal ultrasonography were performed in seven patients and were unremarkable in all. Cerebrospinal fluid was collected from the cerebellomedullary cistern in 13 dogs (Appendix 1). The mean (SD) and median (range) nucleated cell count was 1.99 cells/uL (2.06) and 1 cells/uL (0 to 8 cells/uL), respectively. The nucleated cell count was elevated in two patients (n = 2, 14%), with 6 and 8 cells/uL (reference range 0-5 cells/uL)

respectively. The nucleated cellular population consisted in scattered small/medium lymphocytes and monocytes in all cases, apart from Case 14 were the main population of cells were hypersegmented non-degenerated neutrophils. The mean (SD) and median (range) CSF total protein were 0.30 g/L (0.17) and 0.25 g/L (0.19 to 0.80 g/L), respectively. The total protein was elevated in one patient (n = 1, 7%; reference range 0-0.35 g/L; Case 14). Polymerase chain reaction for canine distemper virus, *Toxoplasma gondii* and *Neospora caninum* were negative in blood and CSF in all dogs tested (n = 9, 64%).

Treatment and Follow-up

The treatment and follow-up information is detailed in Appendix 3. Anti-inflammatory to immunosuppressive doses of systemic corticosteroid (prednisolone at 1 mg/kg once to twice daily) was started at presentation in seven dogs (n = 7, 50%). Only two dogs showed improvement of the clinical signs while under systemic corticosteroid treatment (n = 2, 29%; Cases 4 and 14). Case 10 developed severe gastrointestinal side effects within the first week of treatment and the medication was discontinued at that point. The neurological signs in this dog improved three weeks after the systemic corticosteroid treatment was discontinued. Case 9 showed improvement of the clinical signs three months after discontinuation of the systemic corticosteroid treatment. Furthermore, three dogs without systemic corticosteroid treatment (n = 3, 43%; Cases 6, 7 and 12) improved two weeks to four months after their presentation. In the other seven dogs the clinical signs remained unchanged, three received a course of systemic steroid therapy and four had no treatment.

Six-month follow-up MRI scan was available in two cases (Cases 8 and 14). In case 8, MRI findings at re-examination remained unchanged compared to presentation and clinical signs were not improved. In case 14, MRI at presentation revealed marked enlargement with marked diffuse post-contrast enhancement; however, at re-examination the follow-up MRI showed equivocal enlargement with no post-contrast enhancement (Fig. 5), and clinical signs were improved at that time.

The mean (SD) and median (range) long-term follow-up time was 33.93 months (21.76) and 25 months (12 to 84 months), respectively. The external ophthalmoparesis improved in 64% cases (7/11 dogs) during this period of time and the neuromuscular strabismus resolved. The internal ophthalmoplegia/ophthalmoparesis remained unchanged in 79% cases (11/14 dogs) and partially resolved in 21% cases (3/14 dogs). The mean (SD) and median (range) time to improvement was 5.55 weeks (5.53) and 3.57 weeks (11 days to 4 months) respectively, from the day the clinical signs were first noted. Follow-up of over one year with complete ophthalmic and neurological re-examination by the authors was possible in six cases.

Discussion

This is the first descriptive study of idiopathic oculomotor neuropathy in dogs. The presumptive diagnosis of idiopathic neuropathy was made in all cases based on the failure on revealing an underlying cause. A putative association between cranial neuropathy and hypothyroidism has been stated in the veterinary literature,[18,19] however this is not borne out by other studies.[17,20] None of the dogs of this study showed clinical signs of hypothyroidism and the thyroidal function was normal in the three dogs tested. One case

had been previously diagnosed with hypothyroidism; however, the authors think that there is unlikely association between the hypothyroidism and the oculomotor neuropathy due to the fact that at the time of the onset of the clinical signs (oculomotor neuropathy) the dog did not reveal any clinical signs consistent with hypothyroidism and the thyroid function was controlled. Infectious causes of neuropathy are exceptionally rare in dogs,[2] and none of the dogs tested in this report for canine distemper virus, *Toxoplasma gondii* and *Neospora caninum* were positive. In this study, the lack of clinical deterioration in all cases and the clinical improvement in several dogs might indicate the presence of an underlying oculomotor neuritis with subsequent permanent nerve damage. Furthermore, the MRI findings (CN III enlargement with contrast enhancement) and the mildly elevated cell count in CSF (in two dogs) could support this hypothesis. However, this hypothesis could not be confirmed due to the lack of histopathology and for this reason the term idiopathic neuropathy was adopted. Surgical biopsy at this area carries high operative morbidity due to the location and to the authors' knowledge this surgical approach has not been attempted in dogs.

All cases in this study presented with mydriasis, and only two dogs retained some pupillary response to light at presentation. On the other hand, external ophthalmoparesis was only seen in some dogs. The oculomotor parasympathetic axons are located superficially on the medial side of CN III,[1] subsequently if the neuropathy initiates in this location it is likely that only the parasympathetic component will be affected. The clinical signs were unilateral in all dogs in this study, similar to the reported canine cases of idiopathic facial neuropathy but different to trigeminal neuropathy.[13-17] There are several cases published of unilateral idiopathic trigeminal neuropathy in dogs,[21] however the

majority are bilaterally affected.[13] Bilateral trigeminal neuropathy commonly presents with sudden inability to close the mouth;[13] on the other hand, unilateral trigeminal neuropathy may only manifest with unilateral transitory masticatory muscle atrophy.[2] Subsequently, it is possible that unilateral cases of trigeminal neuropathy of the mandibular branch are overlooked by owners and veterinarians if the atrophy is mild or transitory. The mean recovery time of motor function was five weeks in the present study, similar to other idiopathic cranial neuropathies;[13,14,16] however, a third of the cases affected with CN III motor dysfunction (4/11 dogs) in our study showed no signs of improvement. This finding differs from trigeminal neuropathy where the motor function recovered in all cases;[13] but similar to facial neuropathy, where resolution of clinical signs was only seen in half of the affected dogs.[14,15,16] Some degree of mydriasis persisted in all cases in our study; however, almost a quarter of patients recovered partial CN III parasympathetic function. Medical treatment with corticosteroids did not appear to alter the course of the disease in this study, even though the dose used and length of course varied. Further studies are required to prove the efficacy of corticosteroids for the treatment of idiopathic oculomotor neuropathy, however corticosteroid therapy does not appear to change the clinical outcome of other cranial neuropathies.[13,22]

A total of 22 cases of canine ophthalmoplegia/ophthalmoparesis (internal, external or both) are published in the veterinary literature.[3-12] Of these 22 cases, only three report isolated CN III deficits,[5,8,10] the rest of the reports describe dogs with multiple cranial nerve dysfunction as part of middle cranial fossa syndrome (also known as cavernous sinus syndrome) or other neurological signs.[3-7,9,11,12] The middle cranial fossa is a paired 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

study. Futures studies could also evaluate the sensitivity and specificity of MRI for detecting CN III abnormalities in dogs with idiopathic oculomotor neuropathy. Moreover, MRI features (including a more objective measurement for cranial nerve enlargement) could be evaluated as prognostic factors for regaining full CN III function. The lack of histopathology was unavoidable due to the non-fatal nature of this condition and the high morbidity that a surgical biopsy could carry due to the location of the lesion. The authors applied stringent inclusion criteria for sampled animals in the current study in order to maximize the likelihood of a true positive diagnosis as much as possible.

In conclusion, findings from the current study supported including idiopathic oculomotor neuropathy as a differential diagnosis for dogs presenting with unilateral ophthalmoplegia/ophthalmoparesis (internal, external, or both) with the absence of other neurological and ophthalmic signs, and with MRI lesions restricted to CN III. These cases can have a good prognosis as the clinical signs do not deteriorate or can even improve without treatment.

List of Author Contributions

Category 1

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

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

(c) Analysis and Interpretation of Data: Roser Tetas Pont, Courtenay Freeman, Elsa Beltran, Ruth Dennis and Claudia Hartley

Category 2

(a) Drafting the Article: Roser Tetas Pont, Elsa Beltran and Courtenay Freeman

(b) Revising Article for Intellectual Content: Roser Tetas Pont, Elsa Beltran, Courtenay Freeman, Claudia Hartley and Ruth Dennis

Category 3

(a) Final Approval of the Completed Article: Roser Tetas Pont, Courtenay Freeman, Claudia Hartley, Ruth Dennis and Elsa Beltran

Acknowledgments

To our colleagues and referring veterinary surgeons for their support, and providing the contact details of their clients and the clinical histories of their patients.

References

1. Evans HE, De Lahunta A. Cranial nerves (Chapter 18) in: Miller's anatomy of the dog, 4th ed. Missouri: Saunders Elsevier 2013;708-730.
2. De Lahunta A, Glass E, Kent M. Lower motor neurone: General visceral efferent system (Chapter 7) in: Veterinary neuronatomy and clinical neurology, 4th ed. Missouri: Saunders Elsevier 2015;162-180.
3. Lee R, Griffiths IR. A comparison of cerebral arteriography and cavernous sinus venography in the dog. J Small Anim Pract 1972;5:225-238.
4. Lewis GR, Blanchard GL, Trapp AL. Ophthalmoplegia caused by thyroid adenocarcinoma invasión of the cavernous sinus in the dog. J Am Anim Hosp Assoc 1984;20:805-812.

5. Valentine BA, Summers BA, de Lahunta A, White CL, Kuhajda FP. Suprasellar germ cell tumors in the dog: a report of five cases and review of the literature. Acta Neuropathol 1988;76:94-100.
6. Theisen SK, Podell M, Schneider T, Wilkiw DA, Fenner WR. A retrospective study of cavernous sinus syndrome in 4 dogs and 8 cats. J Vet Intern Med 1996;10:65-71.
7. Fransson B, Kippenes H, Silver GE, Gavin PR. Magnetic resonance diagnosis: cavernous sinus syndrome in a dog. Vet Radiol Ultrasound 2000;41:536-538.
8. Larocca RD. Unilateral external and internal ophthalmoplegia caused by intracranial meningioma in a dog. Vet Ophthalmol 2000;3:3-9.
9. Hernández-Guerra AM, López-Múrcia MM, Planells A, Corpa JM, Liste F. Computed tomographic diagnosis of unilateral cavernous sinus syndrome caused by a chondrosarcoma. Vet J 2001;174:206-208.
10. Rossmeisl JHJ, Higgins MA, Inzana KD, Herring IP, Grant DC. Bilateral cavernous sinus syndrome in dogs: 6 cases (1999-2004). J Am Vet Med Assoc 2005;226:1105-1111.
11. Webb AA, Cullen CL, Rose P, Eisenbart D, Gabor L, Martinson S. Intracranial meningioma causing internal ophthalmoparesis in a dog. Vet Ophthalmol 2005;8:421-425.
12. Grahn BH, Taylor SM, Sandmeyer LS. Diagnostic ophthalmology. Can Vet J 2007;48:321-322.

13. Mayhew PD, Bush WW, Glass EN. Trigeminal neuropathy in dogs: a retrospective study of 29 cases (1991–2000). J Am Anim Hosp Assoc 2002;38:262-270.

14. Varejao AS, Munoz A, Lorenzo V. (2006) Magnetic resonance imaging of the intratemporal facial nerve in idiopathic facial paralysis in the dog. Vet Radiol Ultrasound 2006;47:328-333.

15. Smith PM, Goncalves R, McConnell JF. Sensitivity and specificity of MRI for detecting facial nerve abnormalities in dogs with facial neuropathy. Vet Rec 2012;171:349-354.

16. Jeandel A, Thibaud JL, Blot S. Facial and vestibular neuropathy of unknown origin in 16 dogs. J Small Anim Pract 2016;57:74-78.

17. Kern TJ, Erb HN. Facial neuropathy in dogs and cats: 95 cases (1975–1985). J Am Vet Med Assoc 1987;191:1604–1609.

18. Jaggy A, Oliver JE, Fergusson DC, Mahaffey EA, Glaus TJ. Neurological manifestations of hypothyroidism: a retrospective study of 29 dogs. J Vet Intern Med 1994;8:328–336.

19. Vitale CL, Olby NJ. Neurologic dysfunction in hypothyroid, hyperlipidemic labrador retrievers. J Vet Intern Med 2007;21:1316-1322.

20. Rossmeisl JHJ. Resistance of the peripheral nervous system to the effects of chronic canine hypothyroidism. J Vet Intern Med 2010;24:875–881.

21. Schultz RM, Tucker RL, Gavin PR, Bagley R, Saveraid TC, Berry CR. Magnetic resonance imaging of acquired trigeminal nerve disorders in six dogs. Vet Radiol Ultrasound 2007;48:101–104.

410 22. Motta L, Altay UM, Skerritt GC. Bell's palsy with concomitant idiopathic cranial
411 nerve polyneuropathy in seven dogs. J Small Anim Pract 2011;52:397.
412 23. Parry AT, Volk HA. Imaging the cranial nerves. Vet Rad Ultrasound
413 2011;52:S32-S41.
414 24. Seruca C, Rodenas S, Leiva M, Peña T, Añor S. Acute postretinal blindness:
415 ophthalmic, neurologic and magnetic imaging findings in dogs and cats (seven
416 cases). Vet Ophthalmol 2010;13:307-314.
417 25. Saremi F, Helmy M, Farzin S, Zee CS, Go JL. MRI of cranial nerve enhancement.
418 Am J Roentgenology 2005;6:1487-1497.
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 T2W	FLAIR	T1W	Degree of contrast enhancement	Appearance of contrast enhancement	Anatomical area of the lesion
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 homogeneous	OF and MCF

438

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

hypointensive; Iso, isointense; MCF, middle cranial fossa; MRI, magnetic resonance imaging; N/A, not available; OF, orbital fissure.

444

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

452

453 **Figure legends**

454

455

456

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

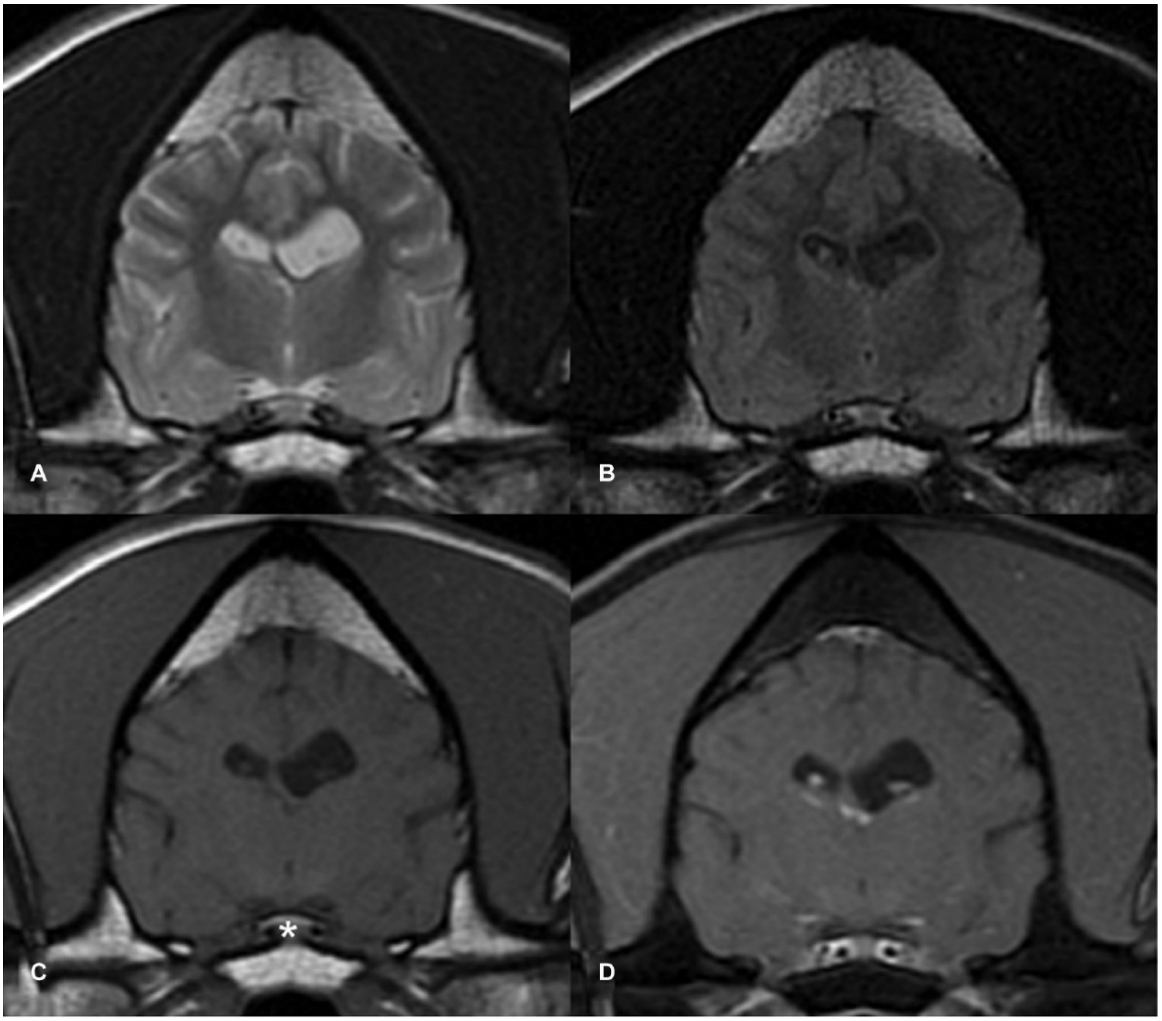

Figure 2. Transverse magnetic resonance images obtained at the level of the pituitary gland (asterisk) in a seven-year-old male neutered Golden Retriever presented with internal ophthalmoplegia and external ophthalmoparesis of the left eye (Case 10). There is equivocal enlargement and isointensity of 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).

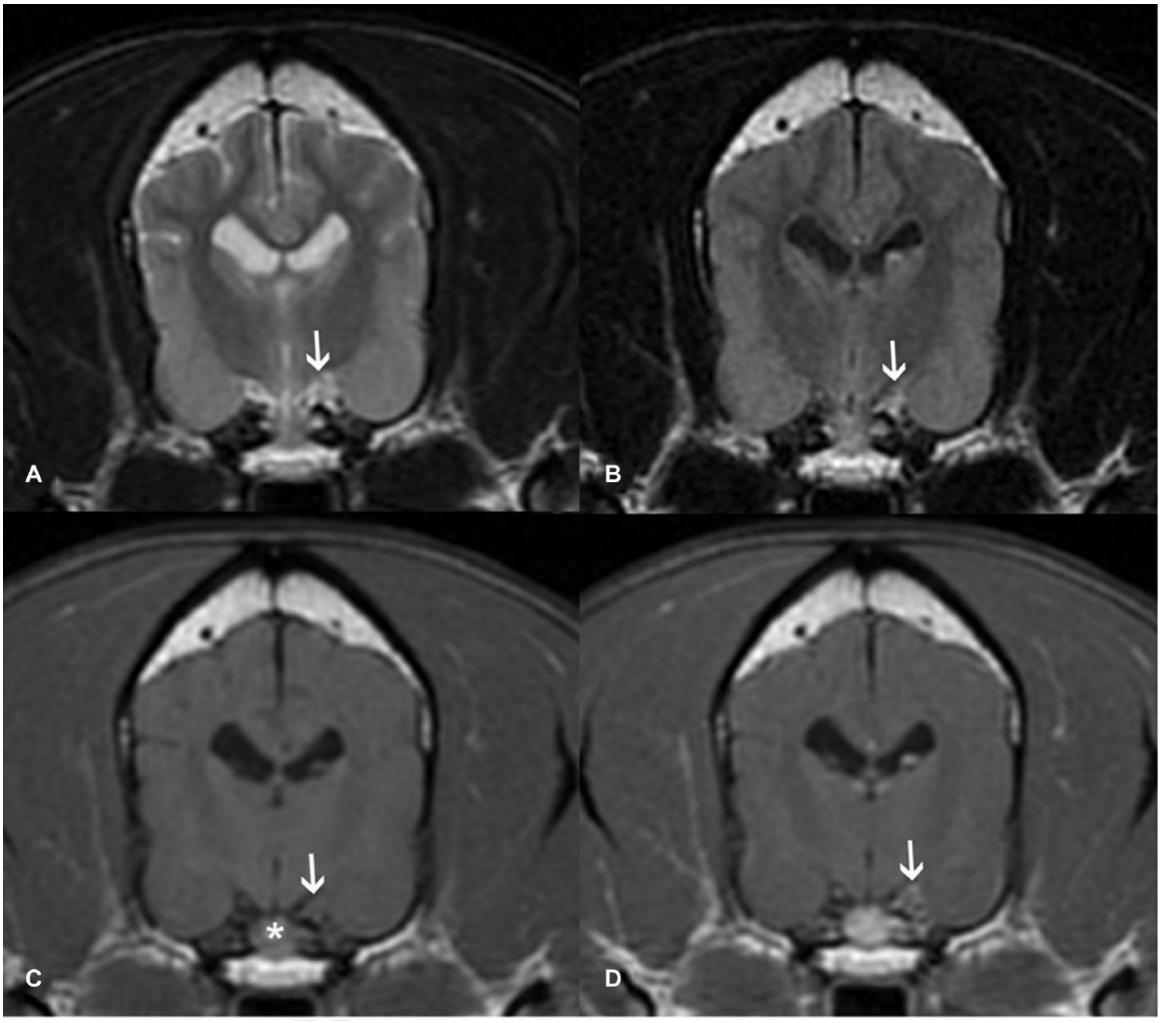

Figure 3. Transverse magnetic resonance images obtained at the level of the pituitary gland (asterisk) in a seven-year-old female neutered Boxer presented with internal ophthalmoplegia and external ophthalmoparesis of the left eye (Case 7). There is mild enlargement of the left oculomotor nerve with 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).

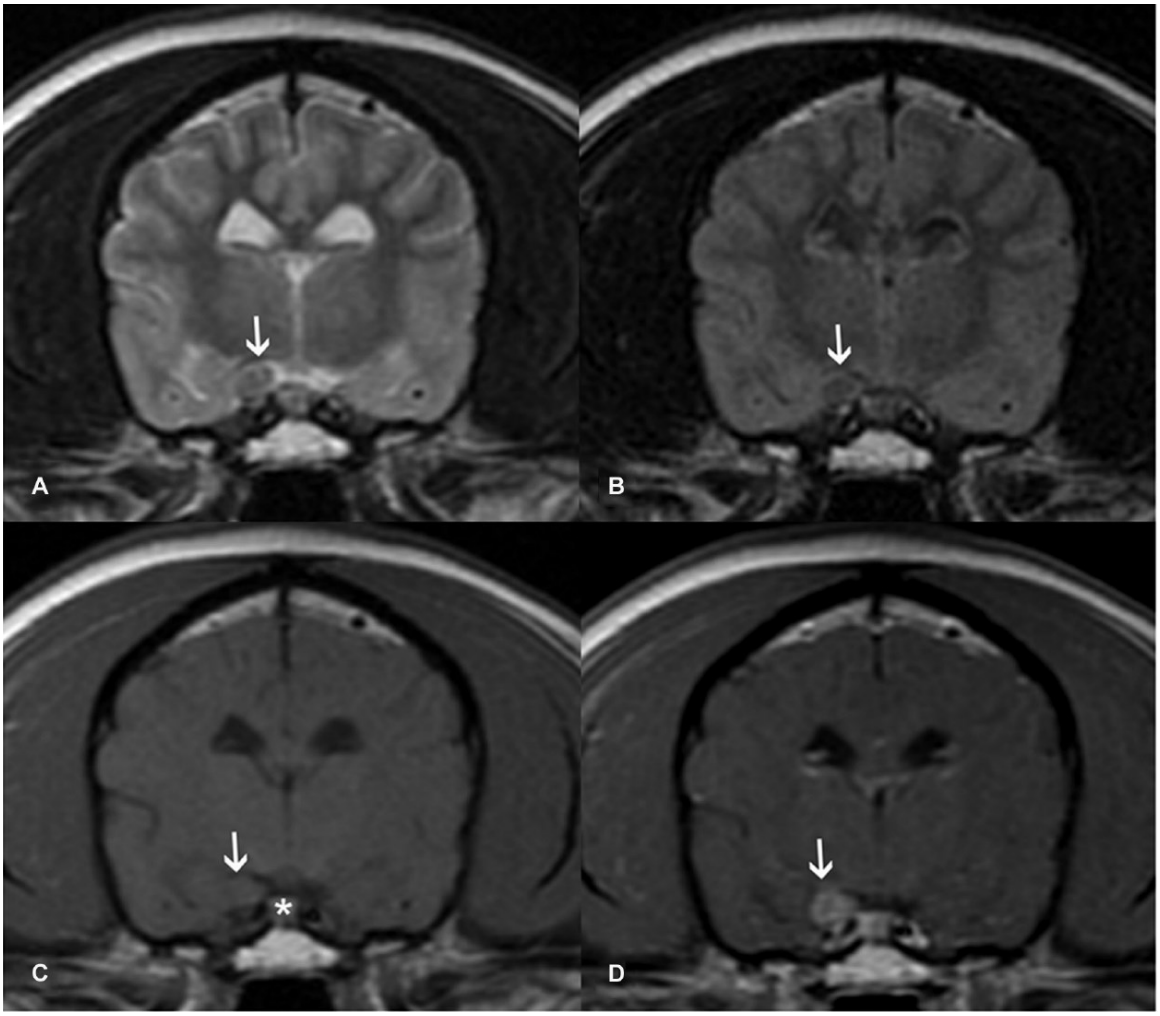

Figure 4. Transverse magnetic resonance images obtained at the level of the pituitary gland (asterisk) in a six-year-old male neutered Beagle presented with internal ophthalmoplegia and external ophthalmoparesis of the right eye (Case 11). There is marked enlargement of the right oculomotor nerve with isointensity on T2W (arrow; A), hypointensity on FLAIR (arrow; B), and isointensity on T1W pre-contrast (arrow; C) with marked focal homogeneous enhancement following contrast administration (arrow; D).

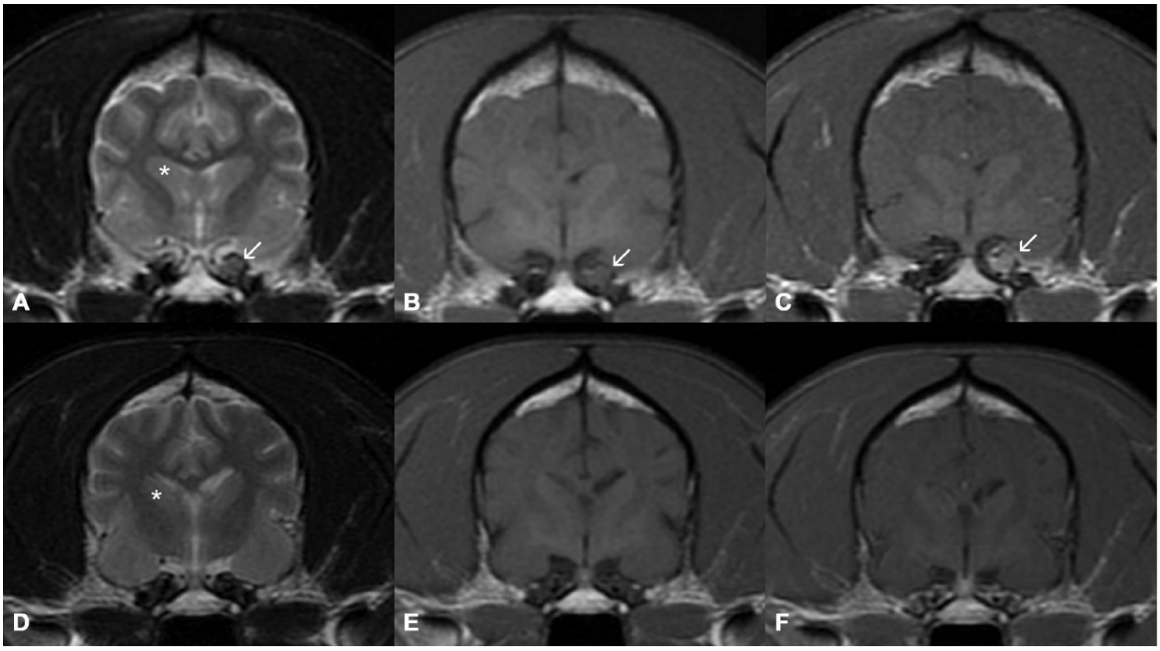

Figure 5. Transverse magnetic resonance images obtained at the level of the head of the caudate nucleus (asterisk) in a three and a half-year-old female neutered Weimaraner presented with internal ophthalmoplegia and external ophthalmoparesis of the left eye (Case 14). There is marked enlargement of the left oculomotor nerve with isointensity on T2W (arrow; A) and isointensity on T1W pre-contrast (arrow; B), with marked diffuse homogeneous enhancement following contrast administration (arrow; C) at presentation. At six-moth follow-up scan, there is resolution of the magnetic resonance findings (D-F).