CASE REPORT

Intracranial meningioma causing internal ophthalmoparesis in a dog

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Abstract

A 10-year-old, spayed female, Irish water spaniel was presented with a 2-week history of anisocoria characterized by mydriasis of the right eye compared to the left eye in ambient light. Ophthalmic and neurological examinations, combined with pharmacological testing, identified a disease process affecting the right parasympathetic nucleus of cranial nerve 3 (CN III) and/or the parasympathetic component of CN III. Magnetic resonance imaging (MRI) identified a mass involving the right midbrain and extending caudally to the rostral border of the medulla oblongata. The dog became comatose within 12 h following MRI and was euthanized. Histopathology identified the intracranial mass as a meningioma.

Key Words: anisocoria, canine, Holmes–Adie syndrome, meningioma, pupillotonia

INTRODUCTION

Internal ophthalmoplegia refers to paralysis of the intraocular muscles, whereas external ophthalmoplegia refers to paralysis of the extraocular muscles.¹ In instances where the intra- and/or extra-ocular muscles are incompletely paralyzed, the term ophthalmoparesis is used. Ophthalmoplegia/paresis, whether internal or external, is rarely described in the veterinary literature.^{2–6} Internal ophthalmoplegia/paresis is a lower motor neuron sign resulting from disease affecting (1) the parasympathetic nucleus of cranial nerve 3 (CN III), (2) the ciliary ganglion, and/or (3) the pre- or postganglionic fibers of the parasympathetic fibers (traveling with CN III) innervating the iris and ciliary body.¹ External ophthalmoplegia/paresis occurs when a disease affects the efferent fibers of CN III that innervate the extraocular musculature.¹ Consequently, most cases of nonpharmacologically induced ophthalmoplegia are combined internal/external (complete) ophthalmoplegia/paresis,^{5,6} and are often observed in conjunction with other neurologic abnormalities (e.g., as is seen with cavernous sinus syndrome,⁵ dysautonomia^{7,8}). There have been three previous reports of internal ophthalmoplegia occurring in the dog.^{2–4} All of these animals were given a presumptive diagnosis of idiopathic pupillotonia (Holmes–Adie-like syndrome). Holmes–Adie syndrome (also known as Adie's syndrome) is a condition described in humans in which internal ophthalmoplegia/paresis is seen without an underlying cause and is associated with decreased or absent

segmental spinal reflexes. Of these presumed cases of canine Holmes–Adie-like syndrome, none of the animals were reported to have altered spinal reflexes and none had undergone advanced imaging. Herein, we report a case of internal ophthalmoparesis resulting from an intracranial meningioma.

CASE REPORT

A 10-year-old, spayed female, Irish water spaniel was referred to the Veterinary Teaching Hospital at the Atlantic Veterinary College (AVC) because of a 2-week history of anisocoria characterized by mydriasis of the right eye compared to the left eye in ambient light. In addition, the owner reported that the dog had appeared 'dizzy' and was sensitive to having the right side of the head touched. Distant examination revealed that the dog was bright, alert, and responsive with no gait abnormalities. Physical examination revealed anisocoria with complete mydriasis of the right pupil. As well, the right external ear canal was erythematous. Physical examination was otherwise unremarkable. Cytological analysis of a swab-collected specimen from the right external ear canal provided a diagnosis of mild otitis externa. The right eye had a very sluggish and incomplete direct pupillary light reflex (PLR) and an absent consensual PLR. The left eye had positive direct and consensual PLRs. The remainder of the neurological examination was unremarkable. Complete ophthalmic examination revealed no abnormal findings. Differential diagnoses for the dilated right pupil included

internal ophthalmoparesis as a result of primary intraocular muscle disease, pharmacological dilation of the right eye, and neoplastic or inflammatory disease affecting the parasympathetic nucleus of CN III or the efferent components of the parasympathetic fibers innervating the right eye. Because the condition was unilateral and there was no history of topical sympathomimetic or parasympatholytic drug therapy, pharmacologically induced mydriasis was excluded as a possible cause of this dog's symptoms.

A complete blood cell count, serum biochemistry profile, and thoracic radiographs were performed and revealed no abnormal findings. It was presumed that the right otitis externa may have accounted for the history of the dog being reluctant to having the right side of the head manipulated. The dog was treated with 2% Burow's otic solution (Burosol[®], Stiefel Canada Inc., Montreal, Quebec, Canada) with 1% hydrocortisone for treatment of the right otitis externa. The owners were advised to monitor the dog's clinical signs for 1 week, followed by consultation with a veterinary ophthalmologist. The owners were instructed to immediately return for further diagnostic work-up should the clinical signs worsen.

One week following initial presentation to the AVC, the dog developed progressive clinical signs. The dog was brought to the original referring veterinarian because of gait abnormalities, drooping of the lower eyelids, prolapse of the nictitating membranes bilaterally, and bilateral ocular and jaw pain. The referring veterinarian presumptively diagnosed masticatory myositis and prescribed 1 mg/kg prednisone PO q 24 h.

One month following commencement of systemic corticosteroid therapy, the dog was returned to the AVC. The owners reported that the prednisone resulted in immediate improvement of the dog's clinical signs, including resolution of the right mydriasis. However, 2 weeks later, the owners began to notice recurrent mydriasis of the right pupil, and described the dog as having a facial droop, and an ataxic gait. Physical and neurological examinations were, however, unremarkable except for anisocoria with the right pupil being mydriatic compared to the left. A complete ophthalmic examination was performed, including neuro-ophthalmic examination (including menace response and dazzle, palpebral, direct and consensual pupillary light, and oculocephalic reflexes), Schirmer tear test (Schirmer Tear Test Strips; Alcon Canada, Mississauga, Ontario, Canada), fluorescein dye (Fluor-I-Strip AT; Ayerst Laboratories, St. Laurent, Quebec, Canada) application, applanation tonometry (Tonopen XL; Biorad Ophthalmic Division, Santa Clara, California, USA), followed by pupillary dilation using 1% tropicamide (Mydriacyl[®], Alcon Canada, Mississauga, Ontario, Canada), and slit-lamp biomicroscopy (Kowa SL-14; Kowa, Tokyo, Japan) and indirect ophthalmoscopy (Keeler All Pupil Indirect; Keeler Instruments, Inc., Broomall, PA). The ophthalmic examination revealed anisocoria characterized by right mydriasis; the anisocoria worsened in bright light. The right pupil was fully dilated and had a subtle, sluggish, and in-

complete, direct PLR with an absent consensual PLR. There were no signs of orbital disease; the remainder of the ophthalmic examination was otherwise unremarkable. The dog returned to the AVC 48 h later for pharmacological testing to help determine the cause of the right internal ophthalmoparesis. Pharmacological testing was performed using 0.1% pilocarpine (Isopto-carpine 1%, Alcon Canada, Mississauga, Ontario, Canada; diluted to 0.1% with eyewash) at one drop applied on both eyes. Response to this dilute solution of pilocarpine (i.e., miosis of the pupils) was monitored every 5 min for 25 min then every 10 min until pupillary constriction occurred. Pilocarpine administration resulted in miosis of the right abnormal pupil 35 min after drug administration. Both pupils were becoming miotic by 45 min following drug administration, although the right pupil was more miotic than the left pupil. The results of the pharmacological testing excluded disease affecting the right iris sphincter muscle and provided a neuroanatomic diagnosis of the right parasympathetic nucleus of CN III and/or preganglionic, postganglionic, or ganglionic lesion of the efferent parasympathetic fibers innervating the right eye. Differential diagnoses at this time included neoplastic or inflammatory disease affecting the parasympathetic nucleus of CN III and/or the efferent components of the parasympathetic fibers innervating the right eye. Magnetic resonance imaging (MRI) of the dog's brain and orbit was recommended to identify the cause of the internal ophthalmoparesis. The owner's elected to taper the dosage of oral prednisone and return to the AVC for further work-up.

One month later the dog was no longer receiving prednisone and was returned to the AVC for further work-up. Clinical findings remained unchanged since last examination; as such, an orbital lesion affecting the ciliary ganglion was deemed unlikely. Thoracic radiography and abdominal ultrasonography were performed to screen for underlying metastatic neoplasia, and revealed no abnormal findings. MRI of the dog's brain and orbit was used to identify a primary brain, and less likely, orbital lesion.

MRI of the dog's brain revealed a mass that was isointense to slightly hyperintense compared to the surrounding brain parenchyma on the T1-weighted image sequence (Fig. 1). The mass was found to be closely associated with the ventral portion of the cranial vault and caused compression of the right ventral portion of the midbrain extending cranially to the right ventral border of the diencephalon and caudally to the rostral border of the medulla oblongata (Fig. 2). There was evidence of a midline shift directed to the left with left lateral ventriculomegaly. The T2-weighted image sequence revealed the mass was well circumscribed and hyperintense to the surrounding brain parenchyma (Fig. 3). Contrast-enhanced T1-weighted images revealed a strong and uniform contrast enhancement of the mass (Fig. 4).

The dog recovered uneventfully following general anesthesia. Approximately 12 h following anesthesia, however, the dog became acutely nonresponsive to external stimuli and was euthanized upon the owners' request. Postmortem examination

Figure 1. T1-weighted MR axial image of the dog's brain. Note the large mass (asterisk) at the level of the midbrain that is slightly hyperintense to the surrounding parenchyma. Also note the left ventriculomegaly.

Figure 2. Gadolinium-enhanced T1-weighted sagittal MRI of the dog's brain. Note the mass (asterisk) extends from the diencephalon to the rostral medulla. The mass is well delineated and causing significant compression of the brainstem.

was performed and histopathologic analysis of the intracranial mass provided a diagnosis of meningioma (Figs 5 and 6).

DISCUSSION

Internal ophthalmoplegia/paresis results from disease affecting the parasympathetic nucleus of CN III and/or the efferent parasympathetic fibers that travel with CN III and may also be seen in cases of severe primary disease of the iris sphincter muscle. Diseases that have been reported to cause internal ophthalmoplegia/paresis in dogs and cats include infectious or noninfectious causes of meningoencephalitis, intracranial or intraorbital neoplasia, severe senile iris atrophy, or dysautonomia.^{5,7-9} Internal ophthalmoplegia/paresis may, however, result from topical application of parasympatholytic drugs.¹

Figure 3. T2-weighted axial MRI of the dog's brain at the level of the diencephalon. Note the mass (asterisk) is well circumscribed and causing significant compression as evidenced by the midline shift to the left.

Figure 4. Gadolinium-enhanced T1-weighted axial MRI at the level of the midbrain. Note strong uniform enhancement of the mass indicating the mass (asterisk) was highly vascular throughout.

The parasympathetic nucleus of CN III (previously called the Edinger-Westphal nucleus) and the somatic motor nucleus of CN III (controls extraocular muscles) are both found within the midbrain just ventral to the mesencephalic

Figure 5. Brain stem. There is infiltration of the subarachnoid space by a neoplastic expansile mass composed of moderately cellular, irregular lobules of cells (H&E).

Figure 6. The neoplastic mass is composed of polygonal cells with scant eosinophilic cytoplasm forming irregular lobules, with focal pseudopalisading. There is a moderate fibrovascular stroma (H&E).

aqueduct.¹⁰ Efferent parasympathetic fibers (preganglionic) travel with somatic efferent fibers of CN III and leave the midbrain via the orbital fissure and travel with CN III within the orbit.¹⁰ The preganglionic parasympathetic fibers synapse on second-order parasympathetic neurons (postganglionic) within the ciliary ganglion located just caudal and medial to the optic nerve.¹¹ Considering the close proximity of the parasympathetic neuronal cell bodies and axons with the somatic motor nucleus and efferent axons of CN III, internal ophthalmoplegia/paresis is rarely seen in the absence of external ophthalmoplegia/paresis, if one excludes pharmaco-

logical causes. In addition, most dogs and cats with ophthalmoplegia/paresis also have evidence of disease affecting CNs III–VI.^{5,9} The constellation of neurological deficits attributed to disease affecting CNs III–VI is known as cavernous sinus syndrome.^{5,9} This syndrome receives its name based on where these cranial nerves are located within the cranial vault. Most dogs and cats presenting with cavernous sinus syndrome have intracranial neoplasia or intracranial inflammatory disease.^{5,9} Our dog did not demonstrate neurological signs consistent with cavernous sinus syndrome. Additionally, this animal did not present with signs consistent with disease affecting the somatic efferent component of CN III (external ophthalmoplegia/paresis) as has been previously reported in another dog with intracranial meningioma.⁶ Based on the extent of the meningioma seen in the present case, it was surprising that internal ophthalmoparesis was this dog's only documented clinical sign during repeated clinical examination.

Meningiomas are one of the most commonly encountered intracranial neoplasms of dogs. Approximately 35–45% of all intracranial neoplasms in dogs are meningiomas.^{12–16} Meningiomas are thought to arise from arachnoidal cells.¹⁷ Consequently, meningiomas can be found in the brain and spinal cord. In addition, meningiomas have been found in the orbit and are thought to arise from either the optic nerve sheath or by extension from an intracranial site.¹⁸ Although meningiomas may arise anywhere throughout the neuraxis, 82% are found intracranially, 15% occur intraspinally, and 3% arise within the orbit.¹⁷ In one study, 83% of meningiomas were found to occur in either the rostral or caudal cranial fossa, while only 16% were found occupying the middle cranial fossa.¹² Meningiomas are typically benign yet cause neurological dysfunction by causing compression and evacuation, as opposed to infiltration, of the adjacent neural tissue.¹⁷ This characteristic of meningiomas is evident in the present case as demonstrated by the compressive nature, and resulting midline shift, seen on the MRI. Clinical signs associated with intracranial neoplasia vary with the location of the neoplasm.¹⁶ To the authors' knowledge, this is the first case describing internal ophthalmoparesis as the primary clinical sign resulting from intracranial neoplasia in a dog. Practical therapies for intracranial meningiomas include surgical resection of the mass with or without radiation therapy, or radiation therapy alone.¹⁹ In the present case, therapy was not considered an option because of the dog's acutely progressive neurological deterioration that developed soon after recovery from anesthesia.

A particular condition in humans, referred to as Holmes–Adie syndrome, is a rare idiopathic phenomenon where a loss of parasympathetic input to the pupil results in mydriasis.²⁰ The condition is typically unilateral, but frequently progresses to affect the contralateral eye.²⁰ Neural degeneration of the ciliary ganglion has been reported in human cases of Holmes–Adie syndrome.²¹ Humans with this syndrome will typically have decreased or absent segmental spinal reflexes.²⁰ Holmes–Adie syndrome has sometimes been associated with bacterial

or viral infections.²²⁻²⁵ Three previous reports of suspected Holmes-Adie-like condition have been reported in dogs.²⁻⁴ The tentative diagnosis of a postganglionic Holmes-Adie-like syndrome was made based upon pharmacological testing using 0.1% pilocarpine as is seen in human cases of Holmes-Adie syndrome. Unfortunately, advanced imaging had not been reported in these cases, although one case³ reported no development of other neurological signs 7 months following diagnosis. Traditionally, documentation of denervation hypersensitivity of the iris sphincter muscle has been thought to be useful for differentiating between pre- and postganglionic parasympathetic causes of internal ophthalmoplegia/paresis.⁴ That is, damage to the ciliary ganglion and/or the postganglionic fibers have been thought to result in more rapid and complete miosis of the affected eye compared to the unaffected contralateral eye, following bilateral topical administration of dilute pilocarpine solution. It has been shown, however, that supersensitivity of the iris to pilocarpine is not different between pre- and postganglionic lesions in humans.²⁶ As in humans, our dog demonstrated more rapid and complete miosis of the affected right eye compared to the unaffected left eye in response to dilute pilocarpine and, yet, a preganglionic lesion was diagnosed.

CONCLUSION

This present case highlights that pharmacological testing using topical pilocarpine is useful for identifying whether the mydriasis was the result of primary iris sphincter muscle disease or was neurologic in origin. If severe primary disease of the iris sphincter muscle is present, one would not expect to observe pupillary constriction following topical pilocarpine administration. Given that our dog had an intracranial meningioma causing preganglionic parasympathetic dysfunction, and appeared supersensitive to topical pilocarpine in the affected eye compared to the unaffected eye, it is important that dogs presenting with internal ophthalmoplegia/paresis of neurological origin undergo advanced imaging of their brain and orbit prior to diagnosing idiopathic pupillonia (Holmes-Adie-like syndrome). Considering Holmes-Adie syndrome has a benign clinical course, it is important that potentially life-threatening causes of internal ophthalmoplegia/paresis be investigated in order to provide the client with an accurate prognosis and treatment options.

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