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Extraocular muscle myositis and restrictive strabismus in 10 dogs

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Abstract

Ten cases of uni- or bilateral restrictive ventromedial strabismus in young dogs of different breeds are reported. Clinically, abnormalities were restricted to the extraocular muscles with sparing of the masticatory muscles and limb muscles. This was supported in some cases by imaging studies, electrophysiology, and immunocytochemical assay for antibodies against type 2M fibers. Histologically, there was variable lymphocytic plasmacytic mononuclear cell infiltration and fibrosis. This disorder is similar in many aspects to chronic masticatory myositis with focal myositis and subsequent fibrosis. Surgical correction may restore eye position and vision.

Key Words: dog, extraocular muscles, fibrosis, myositis, strabismus

INTRODUCTION

Strabismus is a rare clinical disorder in the dog. Several canine cases have been reported describing the clinical signs, the surgical technique for correction, and in one case the magnetic resonance imaging.[1–6] Strabismus has been reported to occur in the Shar Pei as a juvenile esotropia with fibrous-like tissue replacing the medial rectus muscle.[6] Other breeds reported to be affected were the Irish Wolfhound and the Akita.[3–4] The purpose of this article is to report the signalment, clinical signs, results of diagnostic tests, surgical therapy, outcome, and histologic appearance of the extraocular muscles of 10 canine cases of strabismus with restrictive eye movements.

MATERIALS AND METHODS

Medical records of 10 dogs from seven different veterinary clinics were reviewed to obtain information on canine strabismus possibly related to a myopathy of the extraocular muscles. Cases were included if a strabismus requiring surgical correction was diagnosed by the attending ophthalmologist, and if histologic specimens of the extraocular muscles were available for further investigation. Data retrieved from the records included breed, age and gender of the affected dog, history, ophthalmologic findings, results of diagnostic tests, and surgical therapy as well as treatment outcome.

Clinicopathologic evaluation included complete blood count, serum biochemistry profile including creatine kinase (CK) and urinalysis (10/10), antinuclear antibodies, rheumatoid factor, and lupus erythematosus (LE) cells (5/10), serum thyroid profile (2/10), serum antibody titers to *Neospora caninum* and *Toxoplasma gondii* (4/10), assays for serum antibodies against masticatory muscle type 2M fibres and nicotinic acetycholine receptors (University of California, San Diego, CA, USA) (3/10), skull radiographs (1/10), orbital ultrasound (3/10), magnetic resonance imaging of the skull (3/10), and electromyography of the masseter and temporal muscles (2/10), and of the ventral and dorsal rectus muscles (1/10).

Biopsies were obtained by an open biopsy procedure from either the ventral rectus ($n = 6$), ventral oblique ($n = 2$), or medial rectus ($n = 4$) muscles. The tissues were either immersed in 10% formalin (8/10) and paraffin embedded, or flash frozen in isopentane precooled in liquid nitrogen (3/10) and stored at 80 °C. Fresh frozen muscle biopsies were processed by a standard panel of histochemical stains and reactions.[7] Immunocytochemistry was performed using staphylococcal protein A horseradish peroxidase directly on the fresh biopsy sections. Pathological abnormalities within the extraocular muscle biopsies were evaluated by one of the authors (G.D.S.).

RESULTS

Clinical findings

All cases were young dogs (4 months to 4 years, mean, 21.9 months; median, 24 months) of different breeds (Irish

Wolfhound, $n=3$; Akita, $n=3$; Shar Pei, $n=2$; Golden Retriever, $n=1$; and Dalmatian, $n=1$). Four dogs were females; six dogs were male. Four dogs had bilateral and six had unilateral eye involvement. All patients showed rapid onset of the clinical signs (1 week to 4 months). The patients' data, time since onset, and ocular signs are summarized in Table 1.

The initial ophthalmic examination was similar in all patients. The affected eye(s) were assessed to be enophthalmic and had severe ventral ($n=4$), ventromedial ($n=4$) or medial ($n=2$) strabismus. In most cases the cornea was concealed beneath the lower eyelid showing only superior and temporal conjunctiva within the palpebral fissure (Fig. 1a,b). The affected eye(s) had severe visual impairment due to the degree of deviation of the globe(s). Assessment of voluntary duction was difficult in all cases because of the extreme deviation of the globe(s). Only very limited subtle globe movements were noted. Passive forced duction test was positive in all patients, as the globe(s) could not be sursumducted and/or abducted. Direct and indirect pupillary light reflexes could be elicited in all patients. Due to the profound strabismus intraocular examination could not be performed in four patients.

General examination and complete neurologic examination on all the dogs did not identify any abnormalities or deficits aside from the abnormal globe position(s). Restricted jaw movement, or atrophy or swelling of the temporalis and masseter muscles were not noted in any of the cases. Complete blood count, serum biochemistry profile including CK, and urinalysis were within normal limits in all cases.

Screening for immune-mediated disease by testing for autoantibodies including antinuclear antibodies, rheumatoid factor, and LE cells was negative in five dogs. A serum thyroid profile was found to be normal in two dogs. Serum antibody titers to *N. caninum* and *T. gondii* were negative in three cases. One dog had an IgG titer of 1:64 for *T. gondii* which declined to 1:32 after 4 weeks.

Assays for serum antibodies against masticatory muscle type 2M fibres and nicotinic acetylcholine receptors were negative in three dogs. Skull radiographs revealed no significant lesions in one case. Specific extraocular muscles could not be identified with orbital ultrasonography in three cases. Magnetic resonance imaging in three cases revealed severe globe deviation as well as the absence of normal extraocular muscles in the region of the medial rectus, ventral rectus, and ventral oblique muscles (Fig. 2). To exclude generalized myopathies, electromyography of the masseter and temporal muscles was performed in two cases. These muscles were found to be normal as were ventral rectus and dorsal rectus muscles in one case. One dog received immunosuppressive treatment (prednisone 2.2 mg/kg orally) before surgery; the other nine dogs had not been treated with corticosteroids. All cases underwent reconstructive surgery with biopsies of the affected muscles. The applied surgical techniques, postoperative systemic treatment, number of surgeries performed, and outcome of the cases are summarized in Table 2. All muscle biopsies were performed under direct observation through bulbar conjunctival incisions, and isolation of the anterior portion of the extraocular muscles by blunt dissection.

Pathological changes within all muscle blopsies included various combinations of myofiber atrophy (3/10), myonecrosis (3/10), fibrosis (10/10), and mononuclear cell infiltration (4/10) composed predominantly of lymphocytes and macrophages (Fig. 3a,b). Small numbers of eosinophils were present in two cases. Severity ranged from mild atrophy, mild residual cellular infiltration, and fibrosis to complete replacement of muscle tissue with dense fibrous connective tissue.

DISCUSSION

In this report, we describe a clinical syndrome of severe unilateral or bilateral, ventral or ventromedial strabismus and enophthalmus with marked visual deprivation due to globe deviation in 10 dogs. While a variety of breeds were represented, 8/10 cases were Irish Wolfhounds, Shar Peis, and Akitas. Clinically, abnormalities were localized to the

Table 1. Summary of the 10 dogs presented with extraocular muscle myositis and restrictive strabismus.

Case	Breed	Age	Gender	Eye	Time since onset (weeks)	History/Ophthalmologic findings
1	Irish Wolfhound	4y	F	OU	4	Ventromedial strabismus, first OD then OS, OD only sclera visible,blind, OS rotated nasally
2	Irish Wolfhound	2y	F	OU	4	Medial strabismus OU, blind, full sister of case 3, two related dogs affected
3	Irish Wolfhound	2y	M	OS	6	Ventral strabismus OS, only sclera visible, blind, two related dogs affected
4	Shar Pei, fawn	5m	M	OU	2	Ventromedial strabismus, blind
5	Shar Pei, black	4m	M	OU	3	Ventromedial strabismus, first OD then OS, blind
6	Akita	2,5y	F	OD	16	Ventral strabismus OD
7	Akita	2y	M	OS	12	Ventral strabismus OS, only sclera visible, blind half sister affected OU
8	Akita	2y	M	OD	3	Medial strabismus OD, only sclera visible, blind
9	Golden Retriever	1y	M	OS	4	Ventral strabismus OS, only sclera visible, blind
10	Dalmatian	2y	F	OD	4	Ventromedial strabismus OD, marked enophthalmus OD

Table 2. Summary of the applied surgical techniques, postoperative systemic treatment, number of surgeries performed and outcome of the 10 cases with extraocular muscle myositis and restrictive strabismus.

Case	Surgical technique and systemic treatment	No. of surgeries*	Success/outcome
1	OD: Resection of VRM, VOM and MRM 'tacking' of nictitans to orbital rim Prednisone (immunosuppressive dosage)	OD:2	Good: visual, but enophthalmic; some months later dog developed eosinophilic bronchitis
2	Resection of VOM, anterior transposition of DOM Prednisone (anti-inflammatory dosage)	1	Good: visual
3	OD: Resection of VOM OS: Resection of VRM OU: Anterior transposition of DRM 2. OS: Resection of VRM, excision of nictitans Prednisone and azathioprine (immunosuppressive dosage)	OD:2 OS:1	Good: OS: visual, normal position Poor: OD: ventromedial strabismus
4	OD: Resection of MRM OS: Resection of MRM and VOM OU: stay suture to dorsolateral aspect of orbit 2. OD: Resection of VRM, VOM and ventral aspect of MRM, stay suture Prednisone (immunosuppressive dosage)	OD: 2 OS: 1	Good: visual, eyes in normal position
5	OD: Resection of MRM OS: Resection of MRM and VOM Prednisone (first anti-inflammatory, then immunosuppressive dosage)	1	Good: OD Poor: OS: severe ventromedial strabismus, original position
6	Resection of VRM Prednisone (immunosuppressive dosage)	1	Good: eye in normal position
7	Resection of VRM and VOM, Antibiotics	1	Poor: at first improvement with 30% of cornea visible, 3 months later original position of OS, enophthalmus, small palpebral fissure
8	Resection of VRM and VOM Prednisone (immunosuppressive dosage)	1	Good: visual, eye in normal position
9	Resection of VRM and VOM Prednisone (immunosuppressive dosage)	1	Good: visual, eye in normal position; some months later dog died from unrelated reasons
10	Resection of VRM Prednisone (immunosuppressive dosage)	1	Good: globe remains enophthalmic

*Immunosuppressive prednisone dosage: 2.2 mg/kg SID orally, and anti-inflammatory prednisone dosage: 1 mg/kg SID orally.
VRM, ventral rectus muscle; VOM, ventral oblique muscle; MRM, medial rectus muscle; DOM, dorsal oblique muscle; DRM, dorsal rectus muscle

extraocular muscles with no detectable abnormalities in the masticatory or limb muscles.

Canine extraocular myositis (EOM) has been reported previously and is characterized by a bilateral exophthalmos, breed predilection for Golden Retrievers and Labrador Retrievers, and a lymphocytic/plasmacytic inflammation of all extraocular muscles. Restrictive fibrosis has not been reported as a complication of this syndrome, although most of these prior cases were treated with corticosteroids which may have prevented disease progression to a fibrotic stage. In these cases, a similar type of inflammation and myonecrosis was variably present in the extraocular muscles biopsied at the time of surgery (ventral rectus, medial rectus, and ventral oblique), along with different severity of extraocular muscle fibrosis. As such, it is possible that the restrictive fibrosis reported here might be a chronic form of primary extraocular myositis. If this is the case, the syndrome differs from the previous reports of extraocular myositis in breed predilection, the absence of a clinically apparent acute phase of the disease (exophthalmos), a unilateral presentation in 6/10 cases, and inflammation and myofibrosis which is localized to, or most severe in, the medial or ventral rectus muscles.

There are many similarities between extraocular muscle myositis and masticatory muscle myositis (MMM). In both cases the inflammation is localized to specific muscle groups with sparing of all other muscle groups. It has previously

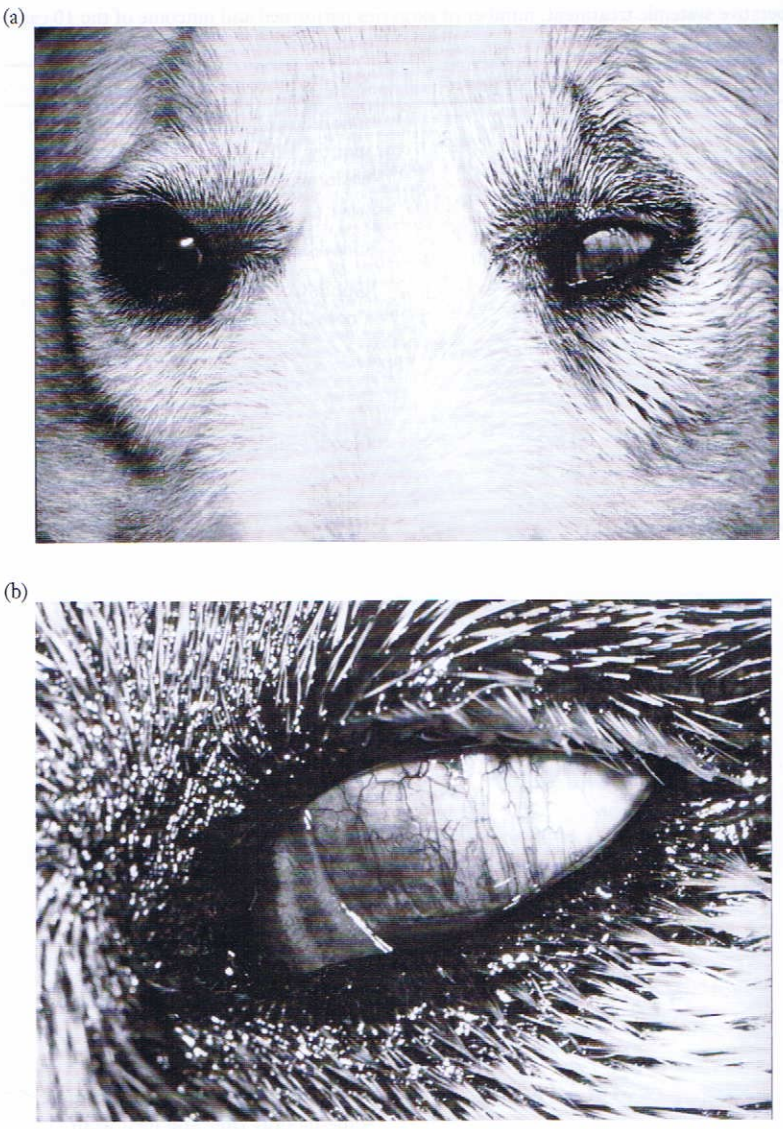

Figure 1. (A) Golden Retriever, 1-year-old male, with left ventral strabismus at initial presentation (case 9). (B) Close up of the left eye, only sclera visible due to severe globe deviation (case 9).

been demonstrated that the muscle fiber types and biochemical properties of the masticatory muscles differ from those of limb muscles.[8–10] In a brief report, fiber types in the extraocular muscles were described by various methods to differ from those of limb and masticatory muscles.[11] In both EOM and MMM there is swelling in the acute phase. In the case of EOM there is exophthalmus and in MMM there is swelling of the masticatory muscles with an inability to open the jaw. Histologically, mononuclear cell infiltration composed of lymphocytes and macrophages with variable numbers of neutrophils and eosinophils predominating. In the chronic stage, there is myofibre destruction and replacement by dense connective tissue resulting in restrictive movement either of the globe as in EOM or the jaw as in MMM. In some cases of EOM and MMM the acute phase may not be observed and dogs present clinically with fibrosis. This appears to be the case in all dogs represented here. None of the dogs showed the typical swelling described for the EOM,[12–13] i.e. strabismus when first presented. Also, EOM is described as a bilateral disease. However, the majority of our cases (6/10) were unilateral. MMM may also present clinically as a unilateral disorder.

Both EOM and MMM have been described as steroid responsive in the acute phase. This suggests an immune-mediated basis for the myopathy. In the case of MMM, autoantibodies have been demonstrated against masticatory muscle type 2M fibers[9] and that muscle fiber type is selectively destroyed. Although not completely characterized, similar unique muscle fiber types within the extraocular muscles could explain the selective involvement and destruction of specific extraocular muscles. The response to corticosteroids is not as favorable in the chronic phase when fibrosis predominates.

Progressive globe deviation has been postulated to be a breed-related disorder of the Shar Pei.[5,6] However in this study not only Shar Peis were affected ($n = 3$) but also Irish Wolfhounds ($n = 3$), Akitas ($n = 2$), a Golden Retriever, and a Dalmatian.

Of the breeds represented with EOM, the Akita and Golden Retriever are at increased relative risk for the

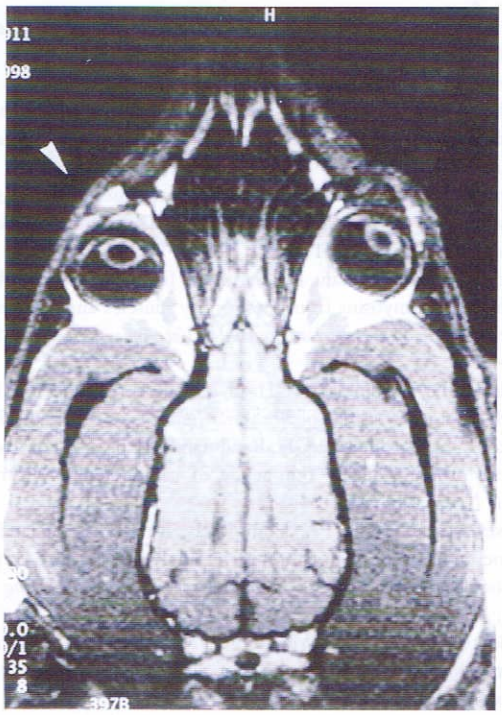

Figure 2. Magnetic resonance imaging of a 4-year-old Irish Wolfhound with right ventromedial strabismus (case 1). TI-weighted image, dorsal orientation. Note the deviation of the right globe (arrow).

autoimmune neuromuscular disorder acquired myasthenia gravis,[14] and masticatory muscle myositis has been observed in Shar Peis (9; G. D. Shelton unpublished data). Three dogs of our series were tested for serum antibodies against masticatory muscle type 2M fibres and nicotinic acetycholine receptors and were negative, thereby ruling out masticatory muscle myositis and mysthenia gravis.

Surgical correction of the globe deviation was attempted in all our cases in which globe deviation was severe and caused visual deprivation. The applied surgical techniques included transsection or resection of the affected muscles (ventral rectus muscle, medial rectus muscle, and ventral oblique muscle) with or without anterior transposition of dorsal rectus muscle and/or dorsal oblique muscle and stay sutures to the orbit. In three cases the muscle resection had to be repeated as the initial procedure was not sufficient to restore vision.

All but one case (case 8) received immunosuppressive systemic therapy that consisted of prednisone, or prednisone and azathioprine. Case 8 was treated by surgery, and received only antibiotics postoperatively. In this case the globe position returned to the original deviation within some weeks. In two dogs the enophthalmus caused marked nictitans prolapse that interfered with vision. In these cases the third eyelid was resected or tacked down to the orbital rim. Of the 13 surgically treated eyes 10 had good results and three had poor results. An interesting aspect of this condition is the return to normal globe position with resection of the affected muscle(s) alone instead of inducing

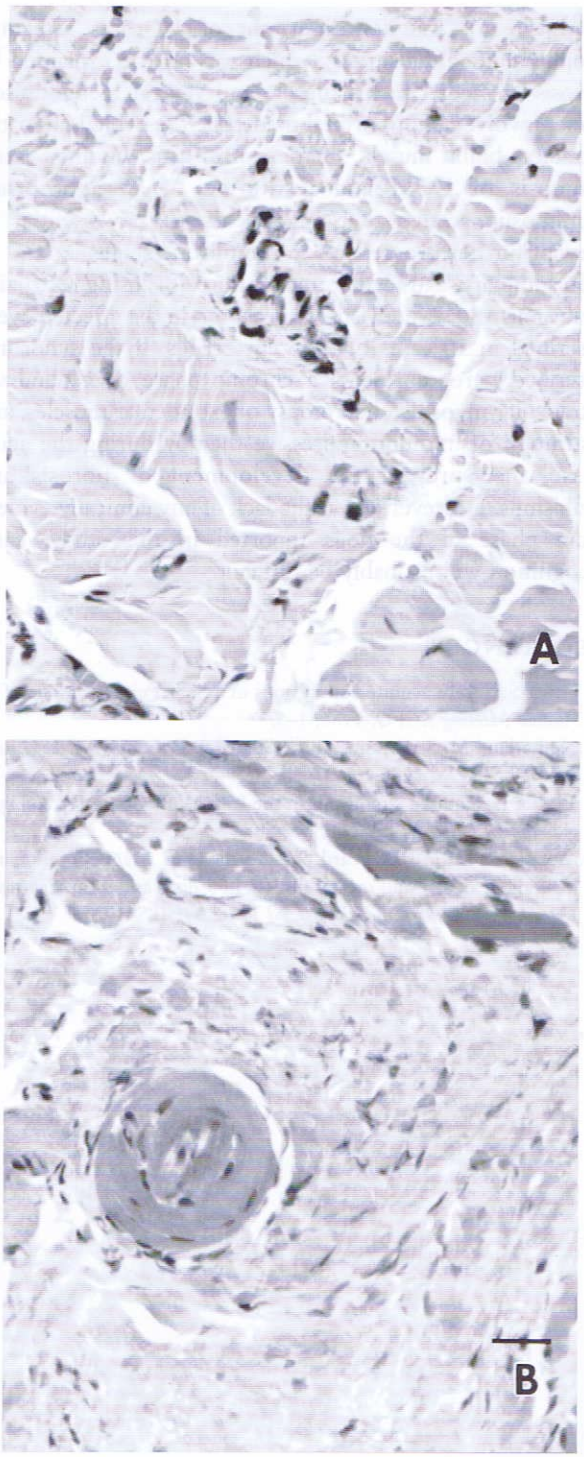

Figure 3. Formalin-fixed biopsy sections from an extraocular muscle of a 2-year-old male Irish Wolfhound with left ventral strabismus (case 3). (A) An accumulation of small numbers of lymphocytes and plasma cells is present with extensive infiltration by relatively immature connective tissue (H&E). (B) In much of the biopsy section, much of the muscle mass has been replaced by interstitial fibrosis. Bar = 10 μm for both (a) and (b).

an opposite strabismus. This might be explained by an atrophy of the lateral rectus muscle and dorsal rectus muscle while fibrosis occurred in the medial rectus muscle and

ventral rectus muscle. Eight out of 10 cases remained enophthalmic after surgery which can not be explained by fibrosis of medial rectus muscle and ventral rectus muscle alone. Involvement of orbital tissue, such as orbital fat or the retractor bulbi muscle, may explain this finding. Early diagnosis of EOM and institution of an appropriate immunosuppressive therapy appears to be essential to prevent fürther progression to the fibrotic stage.

In summary, extraocular muscle fibrosis causing restrictive strabismus and severe visual deprivation in the affected eye is described in 10 cases of different breeds. If the syndrome described here represents a chronic phase of generalized extraocular myositis, then biopsy of extraocular muscles, and institution of immunosuppressive therapy during the acute phase, may prevent the development of fibrosis and strabismus. However, given the lack of any clinically evident acute phase in the dogs reported in this study, early recognition will probably be difficult.

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