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■ Neuro-ophthalmological abnormalities in neurological diseases of dogs and cats: a retrospective study of 114 cases (2010-2015)

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■ Νευροοφθαλμολογικά συμπτώματα σε νευρολογικά νοσήματα του σκύλου και της γάτας: αναδρομική μελέτη 114 περιστατικών (2010-2015)

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ABSTRACT. The current retrospective study includes 99 canine and 15 feline cases with neurologic disease accompanied by neuro-ophthalmological abnormalities (blindness, strabismus, nystagmus, anisocoria, miosis, mydriasis, Horner's syndrome). All cases were presented in the Companion Animal Clinic of the School of Veterinary Medicine – Faculty of Health Sciences (Aristotle University of Thessaloniki) over a six-year period (2010-2015). The most frequent presenting complaints were head tilt (n=22/99) and paresis/paralysis (n=22/99) in dogs and head tilt (n=3/15) and ataxia (n=3/15) in cats. The most common neuro-ophthalmological abnormalities were strabismus (n=55/99) in dogs and anisocoria (n=7/15) in cats. The localization of lesions was found to be multifocal (n=38/99), and focal, in the vestibular system (n=37/99) in dogs, whilst in cats it was solely multifocal (n=6/15). An etiological diagnosis was reached only in 48 dogs and 10 cats; the former were mainly diagnosed with distemper encephalitis (10/48) and congenital hydrocephalus (6/48) and the latter mostly with encephalitis (n=5/10). Neuro-ophthalmological cases reached a 18.24% of the total neurologic case load (n=625) admitted during a six-year period. Neuro-ophthalmological examination as well as the correlation of the observed abnormalities with the overall neurological symptomatology is important for the neuroanatomic diagnosis, the assessment of severity and prognosis of the respected mainly diseases.

Keywords: Neuro-ophthalmology, blindness, miosis, mydriasis, anisocoria, Horner's syndrome, strabismus, nystagmus, dog, cat

ΠΕΡΙΛΗΨΗ. Η παρούσα αναδρομική μελέτη αφορά σε περιστατικά 99 σκύλων και 15 γατών με παθήσεις του νευρικού συστήματος που συνοδεύονταν από νευρο-οφθαλμολογικά συμπτώματα (τύφλωση, στραβισμός, νυσταγμός, ανισοκορία, μύση, μυδρίαση, σύνδρομο Horner), τα οποία προσκομίστηκαν στην Κλινική Ζώων Συντροφιάς του Τμήματος Κτηνιατρικής, της Σχολής Επιστημών Υγείας ΑΠΘ, σε διάστημα έξι ετών (2010-2015). Τα συχνότερα αίτια προσκόμισης των σκύλων ήταν η κλίση κεφαλής (n=22/99) και η πάρεση/παράλυση (n=22/99), ενώ στις γάτες ήταν η κλίση κεφαλής (n=3/15) και η αταξία (n=3/15). Τα συνηθέστερα νευρο-οφθαλμικά συμπτώματα στον σκύλο ήταν ο στραβισμός (n=55/99) και στη γάτα η ανισοκορία (n=7/15). Η νευροανατομική εντόπιση των βλαβών ήταν πολυεστιακή σε 38/99 και εστιακή (αιθουσαίο σύστημα) σε 37/99 σκύλους, αντίστοιχα, ενώ στη γάτα ήταν αποκλειστικά πολυεστιακή. Αιτιολογική διάγνωση τέθηκε μόνο σε 48 σκύλους και 10 γάτες. Στους σκύλους οι συχνότερες παθήσεις ήταν η εγκεφαλομυελίτιδα της νόσου Carrè (10/48) και η συγγενής υδροκεφαλία (6/48), ενώ στις γάτες οι εγκεφαλίτιδες (5/10).. Τα περιστατικά με νευροοφθαλμολογικά συμπτώματα άγγιζαν το 18.24% των συνολικών νευρολογικών περιστατικών της κλινικής (n=625) εντός της περιόδου μελέτης των έξι ετών. Η νευροοφθαλμική εξέταση είναι σημαντική σε κάθε νευρολογικό νόσημα καθώς συνεπικουρεί στον ακριβή προσδιορισμό της νευροανατομικής διάγνωσης αλλά και στη διερεύνηση της σοβαρότητας της νόσου και της πρόγνωσης της.

Λέξεις ευρητηρίασης: Νευροοφθαλμολογία, τύφλωση, μύση, μυδρίαση, ανισοκορία, σύνδρομο Horner, στραβισμός, νυσταγμός, σκύλος, γάτα

INTRODUCTION

Neuro-ophthalmological abnormalities appear more frequently than anticipated in dogs and cats, admitted with neurological disease. The relevant ophthalmological signs may often be overlooked by the practitioners during the routine physical examination. Clinically, they can be grouped into four major categories: a) disorders of vision (central blindness/partial loss of vision), b) disorders of pupil

size and function (miosis, mydriasis, anisocoria, Horner's syndrome), c) disorders of eyeball position (strabismus) d) involuntary eye movements (nystagmus). Other abnormalities in which the nervous system is involved are disorders of blinking (ptosis), third eyelid (protrusion) and lacrimation (Polizopoulou et al., 2001; Penderis, 2004; Lorenz et al., 2011). These abnormalities are evaluated during the neurological examination and should be differentiated

from primary ophthalmological diseases and stress reflex reactions (pain, anxiety). The assessment of all these signs, through a systematic neuro-ophthalmological examination, is important for the precise anatomical localization of the lesion and the final diagnosis (Rucker et al., 2011). In the present retrospective study the incidence of neuro-ophthalmological abnormalities in 99 dogs and 15 cats with neurological disease is reported, as well as their correlation with the most common final diagnoses.

MATERIALS AND METHODS

The study population consisted of dogs and cats admitted with neurologic signs and concurrent neuro-ophthalmological abnormalities, to the Clinic of Companion Animals, School of Veterinary Medicine, Aristotle University of Thessaloniki during a six-year period (2010-2015). The study inclusion criteria were the presence of at least one neuro-ophthalmological sign, along with detailed information from history, clinical and neurological examination, neuroanatomic and etiologic diagnosis.

Data recorded in each case included information on lifestyle, vaccination status, history, presenting complaint(s), physical, neurological and ophthalmological (if available) examination, diagnostic imaging and clinicopathological findings, neuroanatomic diagnosis, etiologic diagnosis. In animals that died or were euthanized pathological examination data (necropsy or/and histopathological examination) were also taken into account if available.

Information from the history, as well as from physical and neurological examination assessed during the evaluation of the overall clinical abnormalities present in the study population. Routine ophthalmological examination was performed in order to differentiate ophthalmological from neuro-ophthalmological signs.

Diagnostic approach regimens included routine clinicopathological evaluation (complete blood counts, serum biochemistry, urinalysis), cerebrospinal fluid (CSF) analysis and diagnostic imaging. The latter included spinal radiographs, ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). Electroretinography was performed

to blind animals for the investigation of the blindness origin. In those cases where a post mortem examination and histopathology findings were available, they were recorded accordingly.

With respect to neuroanatomic lesion localization, cases were grouped as focal (forebrain, brainstem, cerebellum, vestibular system, cranial nerves, spinal cord) and multifocal disorders; an additional category was diffuse neuromuscular disease. Etiologic diagnoses (where available) were classified as congenital-genetic, inflammatory, vascular, traumatic, neoplastic and idiopathic disorders.

RESULTS

Study Population

From a total of 625 (2010-2015) neurologic case records that were reviewed, 114 (18.24%) cases (99 canine and 15 feline) were identified with neuro-ophthalmological abnormalities. Regarding the dogs, 38 were males (6/38 neutered) and 61 females (22/61 neutered). Their age ranged from 0.1 to 19 years old (median 9 years). More specifically, 27 were young (<1 year), 38 middle-aged (1-9 years) and 34 elderly dogs (> 9years). Most of them (n=43, 43.4%) were purebreds, 16 (16.2%) were crossbreds and 40 (40.4%) were mongrels. The most frequently seen breeds were Yorkshire terriers (4/99,4.04%) and Boxers (4/99,4.04%).

Regarding the cats, 8 were males (4/8 neutered) and 7 females (5/7 neutered), of which 6 were young, 5 middle-aged and 4 elderly (age range 0.2-16.5years; median 5.3 years); most of them were domestic short-haired (13/15).

Presenting Complaints

Presenting complaint referred to either the symptoms reported by the owner or referring veterinarian, for which the animal was admitted to the clinic; these were grouped into three categories, depending on the major reason recognized and reported: a) pure neurological, b) neuro-ophthalmological and c) extra-neural symptoms. Forty-six dogs (46.5%) and 7 cats (46.7%) presented a single symptom regardless of its category, 36 dogs (36.4%) and 4 cats (26.7%) two symptoms, 11 dogs (11.1%) and 3 cats (20%) three symptoms, whilst 6 dogs (6.1%) and one cat (6.7%) four symptoms.

Fifty-nine (59.6%) dogs and 7 cats (46.7%) were admitted with only neurological symptoms; head tilt (22/79, 27.8%), paresis/paralysis (22/79, 27.8%) in dogs and head tilt and ataxia (3/8, 37.5% each) in cats were the commonest abnormalities. In addition, three dogs (3%) and one cat (13.3%) presented only for neuro-ophthalmological reasons; blindness was the commonest ophthalmological sign in dogs (4/7, 57.1%) and blindness and palpebral reflex deficits the commonest abnormalities in cats (1/2, 50% each). Curiously, 20 dogs (20.2%) and 6 cats (40%) were admitted only with extra-neural signs, of which weakness (19/42, 45.2%) in dogs and weakness and anorexia (3/8, 37.5% each) in cats (**Table 1**).

Clinical Findings

After a thorough physical and neurological examination, 95 dogs (95.9%) and 12 cats (80%) were found with at least one neurological sign apart from the obvious neuro-ophthalmological abnormalities. The majority of cats (8/15, 53.3%) and some dogs (34/99, 34.3%) were found to have at least one ocular sign. Most of the dogs (73/99, 73.7%) and cats (9/15, 60%) presented additional extra-neural signs.

Physical examination was sufficient for diagnosing common ocular signs such as nuclear sclerosis or conjunctival hyperemia (34/99 - 34.3% in dogs, 8/15 - 53.3% in cats). However, in most of the dogs (29/34, 85.2%) and cats (7/8, 87.5%) an ophthalmological examination was performed due to concurrent ophthalmological disease; the most common ocular disorder in dogs was conjunctivitis (9/34, 26.5%), while in cats there was a variety of disorders. In 34.5% of dogs (10/29) and 57.1% of cats (4/7) with visual disorders an ophthalmoscopy was performed if the owner consented; the most common finding in dogs was optic disc edema (5/10, 50%). Lastly, 13.1% of dogs (13/99) and 30% (5/15) of cats manifested concurrent diseases other than ophthalmological ones.

Neuro-ophthalmological findings

The most common neuro-ophthalmological manifestation in dogs was strabismus (55/99, 55.6%); unilateral (44/55, 80%), positional (36/55, 65.4%) and divergent (20/55, 36.4%) depending on the side or direction, respectively. Second most frequent were pupillary disorders (37/99, 37.4%) with anisocoria (23/37, 62.1%) being most frequently observed.

Horner's syndrome was seen in 7/37 (18.9%) cases, whereas visual disorders were the least common (7/99, 7.1%). A significant number of dogs (31/99, 31.3%) showed more than one neuro-ophthalmological categories (**Table 2**).

Most of the cats manifested pupillary disorders (9/15, 60%), mainly anisocoria (7/9, 77.8%). On the other hand, only one cat (6.7%) manifested unilateral and positional strabismus, whilst the majority of cats (9/15, 60%) appeared more than one neuro-ophthalmological categories (**Table 2**).

Neuroanatomic Diagnosis

Fifty-five dogs (55.5%) showed signs of a focal lesions affecting forebrain (16/55, 29.1%), cerebellum (4/55, 7.3%), brainstem (7/55, 12.7%), vestibular system (21/55, 38.2%), cranial nerves (2/55, 3.6%) and spinal cord (5/55, 9.1%). Multifocal lesions were observed in 38/99 (38.4%) dogs. Six cases (6.1%) had undefined neuroanatomical diagnosis.

Seven cats diagnosed with focal lesions (46.7%), affecting brainstem (3/7, 42.8%), vestibular system (3/7, 42.8%), cerebellum (1/7, 14.3%), cranial nerves (2/7, 28.6%) but none in forebrain. Furthermore, six cats (40%) appeared multifocal lesions absolutely within the brain. In only two cats (13.3%) neuroanatomic diagnosis was not succeeded.

Etiological Diagnosis

In 48 dogs (48.5%) and 10 cats (66.7%) with neuro-ophthalmological abnormalities an etiologic diagnosis could be established. Regarding dogs, the majority of diagnoses (18/48, 37.5%) were inflammatory disorders, mainly distemper encephalitis (66.7%). Ten dogs (20.8%) were diagnosed with congenital disorders, mainly congenital hydrocephalus (60%). Idiopathic peripheral vestibular disease and brain neoplasia appeared less frequently, at a 16.7% (8/48) and 10.4% (5/48) percentage amongst dogs respectively. Least common problems were head trauma (4/48, 8.3%) and vascular disease (ischemic encephalopathy) (3/48, 6.3%) (**Table 3**).

The commonest diagnosis in cats was inflammatory disorders (5/10, 50%), in which facial nerve paralysis, optic neuritis and otitis media – interna (12.7% each). Following, traumatic brain injury and brain neoplasia share an 20% percentage of etiologic

Table 1. Presenting complaints of 99 dogs and 14 cats admitted with neuro-ophthalmological problems (2010 to 2015)

Presenting Complaints (Dogs)	n	%	Presenting Complaints (Cats)	n	%
Neurological Signs	79	79.8%	Neurological Signs	8	53.3%
<i>Only Neurological</i>	59	59.6%	<i>Only Neurological</i>	7	46.7%
Head tilt	22	27.8%	Head tilt	3	37.5%
Paresis/Paralysis	22	27.8%	Ataxia	3	37.5%
Involuntary movements	14	17.7%	Paresis/Paralysis	2	25%
Seizures	13	16.5%	Seizures	2	25%
Ataxia	11	13.9%	Involuntary movements (Circling)	2	25%
Abnormal posture	7	8.9%	Head oscillation	1	12.5%
Dementia	6	7.6%	Dementia	1	12.5%
Muscular spasms and tremors	6	7.6%	Neuro-ophthalmological signs	2	25%
Behavioral change	2	2.5%	<i>Only Neuro-ophthalmological</i>	1	13.3%
Facial paralysis	2	2.5%	Blindness	1	50%
Hypermetria	1	1.3%	Palpebral reflex deficit	1	50%
Urinary incontinence	1	1.3%	Extra-neural signs	8	53.3%
Trismus	1	1.3%	<i>Only extra-neural</i>	6	40%
Dysphonia	1	1.3%	Anorexia	3	37.5%
Neuro-ophthalmological sings	7	7.1%	Weakness	3	37.5%
<i>Only Neuro-ophthalmological</i>	3	3%	Depression	2	25%
Blindness	4	57.1%	Weight loss	1	12.5%
Partial loss of Vision	2	28.5%	Dysuria	1	12.5%
Anisocoria	1	14.3%	Ear neoplasia	1	12.5%
Horner's Syndrome	1	14.3%	Diarrhea	1	12.5%
Extra-neural signs	42	42.4%	Adipsia	1	12.5%
<i>Only extra-neural</i>	20	20.2%			
Weakness	19	45.2%			
Depression	8	19%			
Anorexia	8	19%			
Vomiting	3	7.1%			
Weight loss	3	7.1%			
Respiratory signs (Dyspnea, Coughing, Tachypnea)	2	4.8%			
Salivation	2	4.8%			
Hyperirritability	1	2.4%			
Dysphagia	1	2.4%			
Hypothermia	1	2.4%			
Diarrhea	1	2.4%			
Limb pain	1	2.4%			
Abdominal enlargement	1	2.4%			

Table 2. Incidence and clinical classification of neuro-ophthalmological abnormalities

	N	%	Abnormalities (Dogs)	N	%	N	%	Abnormalities (Cats)	N	%
Disorders of Vision (<i>Central Blindness/ Partial loss of vision</i>)	7	7.1%				1	6.7%			
Disorders of pupil size and function	37	37.4%	Mydriasis (Bilateral)	8	21.6%	9	60%	Mydriasis (Bilateral)	1	11.1%
			Miosis (Bilateral)	6	16.2%			Miosis (Bilateral)	1	11.1%
			Anisocoria	23	62.1%			Anisocoria	7	77.8%
			Horner's syndrome	7	18.9%			Horner's syndrome	3	33.3%
Disorders of Eyeball position (<i>Strabismus</i>)	55	55.6%	Unilateral	44	80%	1	6.7%	Unilateral	1	100%
			Bilateral	11	20%			Bilateral	0	-
			Positional	36	65.4%			Positional	1	100%
			Congruent	4	7.3%			Congruent	0	-
			Divergent	20	36.4%			Divergent	0	-
			ND	3	5.4%			ND	1	100%
Involuntary eye movements (<i>Nystag- mus</i>)	33	33.3%	Positional	4	12.1%	4	26.7%	Positional	1	25%
			Horizontal	27	81.8%			Horizontal	3	75%
			Vertical	3	9.1%			Vertical	1	25%
Disorders of Blink (<i>Ptosis, Palpebral reflex deficit of neurological origin</i>)	24	24.2%	Ptosis (Unilateral)	15	62.5%	5	33.3%	Ptosis (Unilateral)	3	60%
			Ptosis (Bilateral)	0	-			Ptosis (Bilateral)	0	-
			Decreased palpebral reflex (Unilateral)	4	16.7%			Decreased palpebral reflex (Unilateral)	0	-
			Decreased palpebral reflex (bilateral)	4	16.7%			Decreased palpebral reflex (bilateral)	0	-
			Absent palpebral reflex (unilateral)	4	16.7%			Absent palpebral reflex (unilateral)	2	40%
			Absent palpebral reflex (bilateral)	0	-			Absent palpebral reflex (bilateral)	0	-
			ND	4	16.7%			ND	0	-
Disorders of Third Eyelid (<i>Protrusion of neurological origin</i>)	11	11.1%	Unilateral	8	72.7%	5/15	33.3%	Unilateral	5	100%
			Bilateral	3	27.3%			Bilateral	0	-
Animals with more than one categories	31	31.3%		9	60%					

diagnosis (2/10 each); the brain neoplasia consisted of 1 meningioma and 1 metastatic brain neoplasia. At last, one cat appeared with cerebellar hypoplasia (10%) (**Table 3**).

DISCUSSION

In the current study, sudden blindness was the presenting sign in two dogs with optic neuritis, characterized by loss of concurrent bilateral menace response and PLR, whereas from ophthalmoscopy, optic disc edema and hemorrhage were also observed. The first dog had no accompanying neurological signs, while the second one also presented posterior limb paresis and bilateral mydriasis as well. The first case was presumed idiopathic and had full recovery of vision, while in the second one follow-up was not possible. The coexisting neurological signs however are indicative of a multifocal disease, accompanied by optic neuritis, such as distemper or granulomatous meningoencephalitis (Penderis, 2004).

Visual deficit is a frequent clinical sign in congenital hydrocephalus as a result of damage to optical radiation fibers due to the massive dilation of lateral ventricles (Penderis, 2004). Visual disturbances were noted in two hydrocephalic dogs, being the sole deficit in one, and accompanied by other neurological abnormalities (cerebellar ataxia) in the second dog.

Brain tumours are another common cause of blindness, caused by either metastatic infiltration of the optic nerves or chiasma through the cribriform plate or (less commonly) by optic nerve compression (Snyder et al., 2008, Lorenz et al., 2011); currently one dog had metastatic neoplasia affecting the cribriform plate and the visual system as well.

In two other canine cases with visual disturbances one with cerebral and one with vestibular syndrome, the final diagnosis was inconclusive; however, due to normal PLR, ophthalmoscopy and electroretinography findings, it was suspected that the blindness was of intracerebral origin (Millichamp & Dziezyc, 2006; Ofri, 2008a; Lorenz et al., 2011)

In one cat with meningioma the presenting signs were blindness and forebrain signs (seizures). Feline forebrain meningioma may be associated with any of the classic clinical signs seen in patients with any

forebrain disease, including change in mental status, behavior changes, involuntary movements, central blindness (Axlund et al. 2002; Adamo et al., 2003).

Loss of the sympathetic innervation in both orbitals and dilator pupillae muscle could cause a smaller pupil (miosis), smaller palpebral fissure (ptosis – drop of upper eyelid), third eyelid protrusion and enophthalmos (Horner's syndrome). Miosis could also be as a result of iritis, keratitis (through the activation of ophthalmic nerve sensory neurons which cause the oculopupillary reflex) as well as pain in cornea or conjunctiva (Penderis, 2004, de Lahunta, 2009); thus, these should be differentiated from neurological reasons. Similarly, dilation of pupil (mydriasis) is a result of cerebellar medullary nuclei, oculomotor nerve, retinal or optical nerve lesions, but also non-neurological abnormalities of iris (iris atrophy), globe (glaucoma) or anxiety (Penderis, 2004, de Lahunta, 2009). Anisocoria is a result of unilateral miosis or unilateral mydriasis for the reasons explained before, and should be differentiated from morphological anisocoria (aniridia, persistent pupillary membrane) (Scagliotti, 2006).

In the current study, bilateral miosis was found in six dogs; in one case was related to traumatic brain injury (forebrain lesion localization) and in another to distemper encephalomyelitis, accompanied by other neurological abnormalities while vision was normal. A definite diagnosis could not be established in the remaining cases. Pupillary abnormalities are common following head trauma; a result of midbrain tectum compression or forebrain lesion during head trauma is bilateral mydriasis. However, the latter may also be a clinical sign in acute diffuse brain disorders that in itself may not be of any localizing value (de Lahunta, 2009). Only one cat without neurological signs was noticed with miosis which was associated with thromboembolic meningoencephalitis; probably a result of increased intracranial pressure (de Lahunta, 2009).

Eight dogs presented bilateral mydriasis; a final diagnosis was available in three of them and included optic neuritis, idiopathic peripheral vestibular disease and metastatic nasal neoplasia. In the first case, mydriasis was a result of inflammatory optic nerve lesions, while in the second, stress induced sympathotonia due to severe vestibular signs was the

most likely cause. Intracranial tumours may cause miosis initially due to elevated pressure, with subsequent change to mydriasis, as the result of oculomotor nerve compression and subtentorial cortex herniation (Penderis, 2004).

In a cat with FIP encephalitis, blindness and bilateral mydriasis were observed and were associated with ophthalmic signs (chronic uveitis).

Twenty-three dogs presented with anisocoria, however a final diagnosis could be reached in only two cases; in particular, one dog was diagnosed with distemper encephalitis involving the forebrain and brainstem. The second dog had suffered from head trauma and presented with signs of forebrain and central vestibular dysfunction. Anisocoria is commonly seen in traumatic brain injury causing unilateral oculomotor nuclear or nerve contusion or compression in the midbrain area (Platt & Olby, 2004; de Lahunta, 2009). The remaining dogs with anisocoria were tentatively diagnosed as primary (structural) encephalopathies, however further diagnostic investigation was hampered by financial constraints.

Of the seven cats with anisocoria, two presented pontomedullary syndrome signs attributed to head trauma and otitis media-interna, respectively. Inflammation in the middle and inner ear may be accompanied by peripheral vestibular system dysfunction due to involvement of the receptors in the inner ear, as well as damage to the postganglionic sympathetic neurons innervating the smooth muscle of the eyelid, periorbita, and iris dilator muscle. This may result to anisocoria, as well as Horner's syndrome (de Lahunta, 2009; Kent et al., 2010).

Of the 7 dogs with Horner's syndrome, two were diagnosed with distemper encephalomyelitis and one with brachial plexus injury. Myelitis due to distemper is a possible cause of Horner's syndrome, if the cervical and cranial thoracic spinal cord segments is involved (Penderis, 2004). Brachial plexus injury and associated damage to the sympathetic innervation of the eye which arises from the first three thoracic segments, is one of the commonest etiologies of Horner's syndrome (Penderis, 2004). In the remaining cases Horner's syndrome was presumed to be idiopathic as no other abnormalities were detected during diagnostic investigation (Ofri, 2008b).

Two of the three cats with Horner's syndrome were diagnosed with metastatic brain neoplasia. One case (intrathoracic tumor) manifested dementia and spastic tetraplegia, whilst the other (ear squamous cell carcinoma) manifested head tilt, circling and tetraparesis.

Strabismus is an abnormal position of the eye, which may be positional (induced when the head is rotated dorsally) or spontaneous (always present) (Sanders, 2016), but also divergent or convergent. Unilateral lesions in oculomotor (divergent), abducens (convergent), trochlear (obvious only in animals with slit pupils) nerves or their nuclei, but also vestibular system (positional/vestibular) can cause extraocular muscle dysfunction and thus strabismus (Polizopoulou & Zavros, 2001; Ofri, 2008b). This strabismus should be differentiated from orbital and muscular disorders that restrict movement of the globe (Ofri, 2008b).

Five dogs with strabismus were diagnosed with distemper encephalitis. Of them, three manifested unilateral positional strabismus, one bilateral and another unilateral divergent positional strabismus. Positional strabismus, along with nystagmus, has been described as the most frequent vestibular signs of distemper (Amude et al., 2007; Amude et al., 2010). Curiously, vestibular strabismus as well as nystagmus have been observed with an episodic and relapsing nature in distemper dogs (Amude et al., 2010).

Four dogs with congenital hydrocephalus manifested bilateral divergent strabismus, whilst in one was bilateral positional. The strabismus in hydrocephalus is usually caused by orbital skull malformations and mechanical compression, rather than to vestibular dysfunction (Polizopoulou & Zavros, 2001; Sanders, 2016), and has been referred to as the "setting sun sign" (Sanders, 2016).

Four dogs diagnosed with idiopathic peripheral vestibular disease presented ipsilateral strabismus, which was positional in three and spontaneous divergent in one case, respectively. In this condition, spontaneous or vestibular strabismus can occur; the latter should be differentiated from a fixed or static strabismus resulting from denervation of CN III, IV, or VI in which the eye remains fixed in a deviated position regardless of the position of the head (Kent

Table 3. Etiologic diagnosis in dogs and cats with neuro-ophthalmological abnormalities

Diseases	Dogs		Etiology (Diagnostic procedure)	Cats		Etiology (Diagnostic procedure)
	n	%		n	%	
Number of etiologic diagnoses (cases):	48	48.5%		10	66.7%	
Congenital & Genetic disorders	10	20.8%		1	10%	
Congenital hydrocephalus	6	60%	3 (u/s), 2 (CT), 1 (necropsy)	-	-	
Syringomyelia/ Chiari-like malformation	3	30%	3 (MRI)	-	-	
Cerebellar abiotrophy/ Cerebellar hypoplasia	1	10%	1 (MRI)	1	100%	
Inflammatory disorders	18	37.5%		6	60%	
Encephalitis	9	50%	6 Distemper (histopathology) 3 Encephalitis (clinical signs & CSF Analysis)	2	33.3%	1 FIP (histopathology), 1 Bacterial encephalitis (culture)
Encephalomyelitis	2	11.1%	2 Distemper (histopathology)	-	-	
Thromboembolic Meningoencephalitis	-	-		1	16.7%	1 (necropsy & hisitopathology)
Myelitis	2	11.1%	2 Distemper (histopathology)	-	-	
Optic neuritis	2	11.1%	2 Idiopathic (clinical signs & ophthalmoscopy)	1	16.7%	1 Inflammatory (clinical signs & ophthalmoscopy)
Facial nerve paralysis	2	11.1%	2 (clinical signs)	1	16.7%	1 (clinical signs)
Postvaccinal Polyneuritis – Polyradiculoneuritis	1	5.6%	1 Postvaccinal reaction (history)	-	-	
Otitis media – interna	-	-		1	16.7%	1 (otoscopy, clinical signs)
Vascular disorders	3	6.3%		-	-	
Ischemic encephalopathy	3	100%	2 (MRI) 1 (clinical signs & history)	-	-	
Traumatic disorders	4	8.3%		2	20%	
Traumatic Brain Injury	3	75%	3 (clinical signs & history)	2	100%	2 (clinical signs & history)
Traumatic brachial plexus rapture	1	25%	1 (clinical signs & history)	-	-	
Idiopathic disorders	8	16.7%		-	-	
Idiopathic Peripheral Vestibular Disease	8	100%	(clinical signs & history)	-	-	
Neoplastic disorders	5	10.4%		2	20%	
Brain neoplasia	5	100%	1 Meningioma, 1 Oligodendroglioma, 1 Metastatic brain neoplasia (histopathology)	2	100%	1 Meningioma 1 Metastatic brain neoplasia (histopathology)

et al., 2010). Unilateral is the most frequent form of strabismus within this disease (Polizopoulou & Zavros, 2001).

Unilateral positional strabismus was observed in two dogs with ischemic encephalopathy, two with primary brain neoplasia and two with syringomyelia/Chiari-like malformation. In ischemic encephalopathy, the presence of positional strabismus – as well as nystagmus – observed in some dogs with thalamic/midbrain infarction may be due to involvement of the vestibular thalamic area and its afferent connections with the brainstem vestibular nuclei (Garosi et al., 2006; Hillock et al., 2006). Similarly, secondary effects of brain tumor such as edema and hemorrhage pressing the midbrain/brainstem can cause cranial nerve deficits and thus strabismus (Sanders, 2016). Syringomyelia and Chiari-like malformation is commonly associated with divergent strabismus, nevertheless it is unclear whether this is oculomotor nerve/muscle paralysis or related to orbit confirmation (Rusbridge, 2013). Interestingly, one dog with presumed post-vaccinal polyradiculoneuritis manifested bilateral divergent strabismus, a syndrome that has been described (Schrauwen & Van Ham, 1995; Gehringa & Eggarsb, 2001; Quiroz Rothe et al., 2005). Its pathogenesis could be related with the muscle atrophy, as also seen in Guillain-Barré syndrome in people. In the latter complete ophthalmoparesis or limitation of eye movements due to symmetric CN V paralysis have been reported (Gurwood & Drake, 2006). In canine polyradiculoganglioneuritis with neural involvement of trigeminal nerves, clinical signs may include unilateral atrophy and bilateral paralysis of mastication muscles and Horner's syndrome (Panciera et al., 2002).

Bilateral divergent strabismus appeared only in one cat with head trauma, due to intracranial pressure.

Nystagmus may be spontaneous/resting or positional. In vestibular disease it can be horizontal, vertical or rotary depending on the movement direction; nystagmus can also be jerk or pendular depending on the speed of eyeball oscillation (Muñana, 2004). Abnormal nystagmus should be differentiated by physiologic nystagmus which is a result of vestibulo-ocular reflex, conforming the vision axis during head movements (Ofri, 2008b). Lesions that destroy the vestibular system, the brainstem nuclei

(medial longitudinal fasciculus) or neurons of CNs which innervate extraocular muscles (CNs III, IV, VI) cause loss of normal vestibular nystagmus (Ofri, 2008b; de Lahunta, 2009).

Seven dogs with idiopathic peripheral vestibular disease (IPVS) presented abnormal nystagmus (6 horizontal, 1 vertical); the most common form of nystagmus in IPVS is horizontal, but occasionally rotary may appear (Polizopoulou et al., 2006; Ofri, 2008b).

In addition, three dogs with presumed ischemic encephalopathy manifested abnormal nystagmus (3 horizontal). The presence of nystagmus – especially positional – is related to thalamic/midbrain infarction and thus due to involvement of the vestibular thalamic area and its afferent connections with the brainstem vestibular nuclei (Garosi et al., 2006).

Two dogs with primary brain neoplasia (1 vertical, 1 positional), two with distemper encephalomyelitis (2 horizontal) and one with head trauma manifested abnormal nystagmus (1 horizontal). All three diseases may affect the central vestibular pathways causing horizontal, vertical or rotary nystagmus, as well as positional (Ofri, 2008b). Diencephalic (cerebellopontine angle) damage in meningiomas may lead to vestibular signs as the thalamus functions as a relay station for afferent vestibular inputs to the cortex (Motta et al., 2012) or meningiomas located in the cerebellopontine angle are often associated with clinical signs of paradoxical vestibular syndrome (Adamo et al., 2004).

Two hydrocephalic dogs were found to have vertical nystagmus. Occasionally, when hydrocephalus is associated with fourth ventricle enlargement, there may be pronounced vestibular dysfunction (Penderis, 2004). Lastly, an American Staffordshire Terrier with hereditary cerebellar abiotrophy presented abnormal nystagmus; this is due to the cerebellar degeneration and necrosis cerebellar and vestibular syndromes are manifested (March, 2006).

In cats, one with vestibular disease of unknown etiology and one with head trauma presented horizontal nystagmus, whilst one with FIP encephalitis presented positional. FIP-associated granulomas occasionally result in obstruction of cerebrospinal fluid drainage (secondary hydrocephalus) (Sherding, 2006).

CONCLUSION

Neuro-ophthalmological abnormalities often confuse the clinicians and may be misinterpreted or masked by concurrent extra-neural signs that may hamper diagnosis. Moreover, there is overlapping of ocular with neuro-ophthalmological manifestations that further hamper the diagnostic approach. Understanding the pathophysiological mechanisms of these abnormalities is challenging. However, a basic knowledge of underlying neuroanatomy could assist to the precise localization of lesions, speculation on differential diagnosis and prognosis, and improving the chances to reach a final diagnosis or even preven-

tion/treatment. As shown in the current study, neuro-ophthalmological cases reached a 18.24% of the total neurologic case load, admitted during a six-year period. Therefore, represent a significant number of cases, which should not be ignored.

CONFLICT OF INTEREST STATEMENT

None of the authors of this manuscript has a financial or personal relationship with other people or organizations that could inappropriately influence or bias its content. ■

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